



Under the patronage of Anne Fagot-Largeault

Opening speech: Jean Gayon

25 junior researchers

Senior talks:
Derek Bolton
Giovanni Boniolo
Maël Lemoine
Peter Machamer
Norbert Paul

Thematic workshops:
Elodie Giroux
Alain Leplège
Michel Morange

Université Paris 1
12, Place de la Sorbonne
75005 Paris

INTERNATIONAL ADVANCED SEMINAR IN PHILOSOPHY OF MEDICINE

“UNITY AND AUTONOMY IN THE PHILOSOPHY OF MEDICINE”

JUNE 20-21-22, 2013

iaspm.sciencesconf.org



Book of abstracts

CFC - "Unity and autonomy in the philosophy of medical science"	4
General information.....	6
Scientific program	8
Session 1 – Are there specific epistemological issues in clinical medicine? Chair – Norbert Paul	10
Session 2 – How history, sociology and ethics can influence epistemology of medical knowledge? Chair – Giovanni Boniolo	16
Session 3 – Can and should philosophy of medicine free itself from philosophy of biology? Chair – Maël Lemoine	22
Session 4 – Which methodological approaches for philosophy of psychiatry? Chair – Derek Bolton	31
Session 5 – How does medicine combine different types of evidence and different types of explanations ?	37
Thematic Workshops IASPM 2013	45

CFC - "Unity and autonomy in the philosophy of medical science"

Context

Philosophy of medicine is a growing, widely investigated field whose foundations as a discipline are still under construction. Apart from the *International Philosophy of Medicine Roundtable*, some less topic-specific seminars such as *the Advanced Seminar in the Life Sciences*, and some graduate programs, there are few specialized international venues that allow for a common educational background amongst students of this field.

A new event in philosophy of medicine

To this end the **International Advanced Seminar in the Philosophy of Medicine** (IASPM) aims to offer a biennial international three-day event for PhD students and early-career researchers in philosophy of medicine to meet, exchange ideas, acquire a general background in the discipline and present their work. Five institutions that have teaching programs or research activity in philosophy of medicine will organize this event together: the Institut d'Histoire et de Philosophie des Sciences et des Techniques (CNRS/University Paris 1 Panthéon-Sorbonne/ENS), the Institute for the History, Philosophy and Ethics of Medicine (Johannes Gutenberg University Mainz), the European School of Molecular Medicine (in collaboration with the research group Biomedical Humanities at the European Institute of Oncology, Milan), the Center for Humanities and Health at King's College in London and the Department of History and Philosophy of Science at the University of Pittsburgh.

The first meeting of this conference will be held in Paris in 2013, at the Institut d'Histoire et de Philosophie des Sciences et des Techniques, from June 20 to June 22. The seminar will gather twenty-six speakers, five senior researchers and twenty-one junior researchers in philosophy of medicine, coming from the organizing universities and others.

Topic

For the first meeting of this three-day event, the main theme will be "***Unity and autonomy in the philosophy of medical science.***" Indeed, philosophy of medical science is not limited to the debate over the nature of disease (naturalism versus normativism) anymore and has extended its scope to include: philosophy of evidence-based medicine, philosophy of biomedical ontologies, philosophy of epidemiology, philosophy of psychiatry, and philosophy of medical explanation (models, mechanisms, causation). However, if some of these issues have been the main theme of dedicated books and conferences, most of the time they are separately examined, thus avoiding central questions of conceptual unity between these different fields of research. For instance, do philosophy of evidence-based medicine and philosophy of epidemiology use the same concept of causation? To what extent do philosophy of biomedical ontologies and the debate over the nature of disease appeal to the same concept of natural kinds? Is the philosophy of medical science a variegated collection of separate issues or are there some common conceptual grounds that give unity to this discipline?

But the question of internal coherence in philosophy of medicine is deeply related to the question of its autonomy, both from other fields in philosophy of science and from social studies of medicine. Indeed, on the one hand, it is obvious that these different branches of philosophy of medicine have been considerably influenced by general philosophy of science, philosophy of statistics, and philosophy of biology. While this influence was needed, we may wonder how autonomous philosophy of medicine really is and whether some concepts do, in fact, need to be specifically developed for the medical context. For example, is there such a thing as a medical concept of the gene? Are mechanisms in medicine different from mechanisms in biology? Are explanations in medicine of the same kind as explanations in biology?

On the other hand, stakeholders in philosophy of medical science should probably define more clearly how they relate to, and differ from, social studies of medicine, namely the history and sociology of medicine. Indeed, while philosophy of medical science is usually considered distinct from these disciplines, many philosophers of medicine frequently borrow their methodological tools and little has been said about how this may affect the way they conceptualize their objects.

General information

Topic: “Unity and autonomy in philosophy of medicine” (detailed below), under the patronage of Anne Fagot-Largeault

Time : 20-21-22 June 2013

Location : Centre Panthéon – 12, place du Panthéon – 75005 Paris (Room 1)

Organizing Committee :

Jean Gayon, IHPST, Paris (chair)
Maël Lemoine, University of Tours / IHPST, Paris (co-chair)
Hélène Richard, IHPST, Paris (Phd student)
Marie Darrason, IHPST, Paris (Phd student)

Scientific Committee :

Derek Bolton, KCL, London
Giovanni Boniolo, SEMM, Milan
Anne Fagot-Largeault, Collège de France, Paris
Denis Forest, University Paris 10 / IHPST, Paris
Jean Gayon, IHPST, Paris
Axel Hüntelmann, GTE, Mainz
Maël Lemoine, IHPST, Paris
James Lennox, University of Pittsburgh, Pittsburgh
Peter Machamer, University of Pittsburgh, Pittsburgh
Sandra Mitchell, University of Pittsburgh, Pittsburgh
David Papineau, KCL, London
Norbert Paul, GTE, Mainz
Kenneth Schaffner, University of Pittsburgh, Pittsburgh
James Woodward, University of Pittsburgh, Pittsburgh

Reviewing Committee :

Derek Bolton, KCL, London
Giovanni Boniolo, SEMM, Milan
Maël Lemoine, Université de Tours / IHPST, Paris
Peter Machamer, University of Pittsburgh, Pittsburgh
Norbert Paul, GTE, Mainz

Scientific provisional program (detailed program below) :

5 senior talks
22 early-career researchers talks
3 thematic workshops organized by 3 senior researchers and 3 Phd students

Co-organized by the following research centers :

the Institut d’Histoire et de Philosophie des Sciences et des Techniques, Université Paris 1 Panthéon-Sorbonne / CNRS / ENS
the Department of History and Philosophy of Science, University of Pittsburgh
the Center for Humanities and Health, King’s College,
the European School of Molecular Medicine, in collaboration with the research group in Biomedical Humanities at the European Institute of Oncology, Milan
the Institute for the History, Philosophy and Ethics of Medicine, Johannes Gutenberg University

With the sponsorship of :

CNRS

Université Paris 1 Panthéon-Sorbonne

Collège des Ecoles Doctorales de l'Université Paris 1 Panthéon Sorbonne

Region Ile de France (08.10.18.18.18)

Institut Universitaire de France

Registration :

- Participation to the IASPM is free of charge but there are a limited number of participants and registration is mandatory. So, please register as soon as possible.
- If you are interested in attending the conference, registration is now open on the website of the IASPM: <http://iaspm.sciencesconf.org/registration/index>
- Registration is not required for selected speakers.
- Attendance to the thematic workshop is only for the selected speakers.

Scientific program

JUNE 20		
8h00-9h00		<i>Breakfast and registration</i>
8h30-9h00	Anne Fagot-Largeault Jean Gayon	Welcoming participants and opening speeches
9h00- 12h40	Session 1: Are there specific epistemological issues in clinical medicine?	
9h00-9h40	Norbert Paul	Preliminary remarks on uncertainty, contingency, arbitrariness and other commonly neglected epistemological impairments of clinical problem solving
9h40-10h20	Armand Dirand	Elements of critical reflection upon uncertainty in medicine
10h20-10h40		<i>Coffee break</i>
10h40-11h20	Chris Blunt	Divided we stand; united we fall – the problems of particular patients in public health, epidemiology and health policy
11h20-12h00	Nicholas Binney	Using integrated history and philosophy to inform diagnostic medicine: the case of heart failure
12h00-12h40	Ashley Kennedy	Differential diagnosis: what counts as evidence?
12h40-14h30		<i>Lunch</i>
14h30 -17h30	Session 2: How history, sociology and ethics can influence epistemology of medical knowledge	
14h30-15h10	Giovanni Boniolo	From classical medicine to molecular medicine: only a problem of methods?
15h10-15h50	Stéphanie Van Droogenbroeck	Alternative experimental philosophy meets philosophy of medicine: where sociology has never been before
15h50-16h10		<i>Coffee break</i>
16h10-16h50	Hélène Richard	Analysis of the concept of “intrauterine patient”: history, ethics and epistemology at the crossroads
16h50-17h30	Silvia Camporesi	Adults seeking prescriptions for cognitive stimulants under the rubric of ADHD: a case study in the ‘unity and autonomy’ of Philosophy of Medicine within the Medical Humanities

JUNE 21		
8h30-13h00	Session 3: Can and should philosophy of medicine free itself from philosophy of biology?	
8h30-9h10	Maël Lemoine	Commensalism or mutualism: what is pathophysiology to physiology?
9h10-9h50	Barthélémy Durrive	In what sense are the clinical concept of function and its philosophical rendering “specific”?
9h50-10h30	Jonathan Sholl	Rethinking the Biology-Medicine relation via Phenotypic Flexibility and Robustness
10h30-11h00		<i>Coffee break</i>
11h00-11h40	Pierre-Luc Germain	Symptoms in vivo and in vitro – cellular reprogramming between biology and medicine
11h40-12h20	Gladys Kostyrka	Fighting infectious diseases: how an ecological vision of disease may inform biomedical and therapeutical strategies?
12h20-13h00	Lydia Du Bois	Pathology in context – response to Kingma
13h00-15h00		<i>Lunch</i>
15h00-18h00	Session 4: Which methodological approaches for philosophy of psychiatry?	
15h00-15h40	Derek Bolton	Conceptualizing the medical gaze: definitions of disorder in and around the main psychiatry texts
15h40-16h20	Yazan Abu Ghazal	Schizophrenia or the detours of the history of psychiatry: perspectives from the German psychiatry in the last third of the nineteenth century.
16h20-16h40		<i>Coffee break</i>
16h40-17h20	Kathryn Tabb	Psychiatric objects in research and practice: introducing the RDoc
17h20-18h00	Norman Poole	Meaning and meaninglessness in psychiatric disorders

JUNE 22		
9h00-15h50	Session 5: How does medicine combine different types of evidence and different types of explanations?	
9h00-9h40	Jonathan Fuller	Science, Argument and Clinical trials
9h40-10h20	Hajimé Fujimori	Radical transformation of Chine traditional medicine in Japan – Epistemology in East-Asian traditional medicine
10h20-10h40		<i>Coffee break</i>
10h40-11h20	Marco Annoni	The myth of placebo additivity: taming the efficacy paradox in RCT
11h20-12h00	Jennifer Bulcock	The status of mechanistic evidence in EBM
12h00-14h00		<i>Lunch</i>
14h00-14h40	Lara Keuck	Abstracting and Abstractions in the Medical Science
14h40-15h20	Marie Darrason	Mechanistic and topological explanations in medicine – the case of Network Medicine
15h20-16h00	Lauren Ross	Dynamical models: a type of mathematical explanation un neuroscience and medicine
16h00-16h15		<i>Coffee break</i>
16h15-17h45	Three parallel thematic workshops: <ul style="list-style-type: none"> - Elodie Giroux, Marion Le Bidan: Health and disease concepts: is there still any relevance of their philosophical analysis? - Alain Lépège and Hidetaka Yakura: Knowledge and practice in medicine - Michel Morange and Smail Bouaziz: Plurality of explanatory schemes in medicine 	
17h45-18h00	Maël Lemoine	Closing speech

Session 1 – Are there specific epistemological issues in clinical medicine? Chair – Norbert Paul

Preliminary remarks on uncertainty, contingency, arbitrariness and other commonly neglected epistemological impairments of clinical problem solving

Norbert Paul, Institut für Geschichte, Theorie und Ethik der Medizin, Universitätsmedizin der Johannes Gutenberg-Universität Mainz

To be announced

Elements of critical reflection upon uncertainty in philosophy of medicine

Armand Dirand, Laboratoire de Recherches philosophiques sur les Logiques de l'Agir, Université de Besançon

Nowadays, uncertainty is a fundamental notion in our way of considering medicine, at every level: be it considering our knowledge drawn from medical sciences, applying it to care practicing, or evaluating the therapeutic or ethical issues of a decision, a stakeholder in medicine especially in charge of decision-making has to face uncertainty, though uncertainty may be of different kinds. Uncertainty related to the limits of our academic medical knowledges is indeed different, for instance, from the one conducting a practitioner who is making a diagnosis, considering a treatment or looking to judge the degree of information or freedom of his patient's consent. Medicine thus gathers and structures uncertainty at different scales, different forms and ways of thinking it. From a philosophical point of view, it implies that the reflection on medical uncertainty depends on questionings linked to epistemological issues in theory of knowledge as well as logic of action in general, or ethical action in particular.

A quick review of the way uncertainty has been handled in academic literature (either philosophical, ethical or to some extent, medical) highlights the variousness of possible forms and meanings of this concept as well as the plural questionings related to it. It also shows how authors have particularly paid attention to the inflexion of the concept in the medical context. However, the papers frequent referring to external determinants in the managing of uncertainty does not prevent them from putting aside the question of the unity and specificity of this concept from a global point of view, beyond the plurality of separated approaches. And yet correctly conceptualizing medical uncertainty is crucial. Indeed, if the accuracy and rightness of a medical action or decision strongly depends on the knowledge of the case held by the decision-makers or practitioners, then the uncertain aspects of the case and more importantly the way it impacts our understanding of those cases should be closely taken into account.

A philosophical reasoning on that matter has then to take that diversity of uncertainties into account, without however necessarily reducing the notion to a mere aggregate of alien approaches. Indeed, experience tends to underscore that, in complex medical-decision making, it is difficult to handle separately those different kinds of approaches by abstracting them from all the other determinants that structure the problem. In those cases, and as far as uncertainty is concerned, complexity not only relies on the fact that there are several aspects of uncertainty in the problem, but also differs according to the degree of uncertainty of each kind and the way they can interfere with each other. Thus this complexity seems to rely also on the different associations of uncertainties and their features, leading to consider the concept of medical uncertainty as a plurality of kinds of uncertainty brought together as well as a global concept referring to the result of their association.

In other words, it seems that we can abstract different kinds of uncertainty from a global medical case in order to handle them with the suitable approaches specific to the philosophical field they belong to.

But the transversality that characterizes the philosophy of medicine could also induce the need for a broader point of view afterwards. Medical uncertainty as it is usually thought in Philosophy could be completed by a more synthetic reflection, after analyzing separately each of its components resorting to external philosophical fields. If not, keeping the concept of medical uncertainty split could prevent us from understanding fully what medical uncertainty fundamentally is, both in the plurality of its appearances in the field of medicine and the unity of its global, though structured, impact on our understanding of medical cases, especially in a decision-making outlook.

We shall then question the specificity of medical uncertainty from a global point of view in Philosophy of Medicine, and support a conceptualization of uncertainty in medicine based on the study of global forms of interactions between kinds of uncertainty that characterize and build medical cases. We shall thus begin with a global characterization of the different kinds of uncertainty as seen in the medical field and considered in the academic literature. From then on, we shall consider the way they combine and interact with each other in the experience of complex medical cases, and how a specific degree and kind of uncertainty can influence another. We shall then draw from that some elements of understanding regarding the structure and the functioning of a global conception of medical uncertainty, that is to say the way the concept of uncertainty concretely acts in structuring problems raised by complex medical cases.

Differential Diagnosis and Uncertainty in Medicine

Ashley Kennedy, University of South Carolina

Introduction

Diagnoses in medicine are never certain, but they are based on evidence. However, just what should count as evidence when making a medical diagnosis is not always clear. In particular, the question of whether “evidence for” and “evidence against” should carry equal weight in the process of differential diagnosis is one that is not well addressed in either the medical or the philosophical literature. My aim, then, in this paper is to shed some light on this question via an examination of the use of diagnosis of exclusion in differential diagnosis. Differential diagnosis consists in “the selection of some diagnoses as more probable [...] than others[1],” while diagnosis of exclusion is the practice of settling on one diagnosis by eliminating, or excluding, others. Deciding upon a diagnosis in medicine is thus sometimes made on the basis of positive findings and in other cases (at least partly) upon the basis of negative findings. Knowing how to weight these types of evidence, then, is an important component of clinical practice.

Constructing a Differential

Some medical diagnoses are made on the basis of simple pattern recognition. But in many cases, when a disease or disorder is not immediately recognized in the clinical setting, probabilistic reasoning must be used as an aid in the diagnostic process. Using this method of reasoning, the physician uses the clinical assessment to generate a pretest probability of a possible disease, and then turns to the results of diagnostic testing to generate a posttest probability, which is then compared with thresholds. He or she will do this for several diseases or disorders, thereby constructing what is known as a “differential.” Simply put, a physician decides what to put in a differential by looking at pieces of positive evidence or “evidence for” certain diseases. However, when deciding what to exclude, or take out of a differential, a physician, in many cases might use “negative evidence,” or diagnosis of exclusion. Thus a diagnosis of exclusion depends upon both having positive evidence in the form of the right set of symptoms and negative evidence in the form of having ruled out other diseases or disorders in the differential.

Diagnosis of Exclusion: A case study

To see how evidence is weighed in the process of diagnosis from exclusion, in this section of the paper I will consider the diagnosis of Ménière's disease. The symptoms of Ménière's are vertigo, hearing loss and/or tinnitus. The differential diagnosis of Ménière's disease includes^[2]:

Benign paroxysmal positional vertigo

CNS causes of vertigo

Inner ear

Autoimmune disease

Evaluation of dizziness

Labyrinthitis

Perilymphatic fistula

Tinnitus

Migraine-associated vertigo

Thyroid, thyrotoxic storm following thyroidectomy.

When the above symptoms are present, and these conditions are ruled out, a diagnosis of Ménière's is made. This diagnosis is considered by clinicians to be a diagnosis of exclusion because, as one physician puts it, "If the cause of vertigo, hearing loss and/or tinnitus can be determined, Ménière's is not diagnosed."^[3]

Analysis

The question I will address in this section is that of the epistemic standing of diagnosis of exclusion. I will argue that a diagnosis from exclusion should not be given the same epistemic standing as diagnosis from inclusion. However, I will argue that this is not because diagnosis from exclusion fails to reveal the mechanism, or cause, behind the disease, but rather, because diagnosis from exclusion is not a diagnosis at all. I will argue that in order to have an epistemically viable diagnosis one must not rely on negative evidential findings. That is, I will argue that only positive evidence counts in favor of a diagnosis and that, therefore, it is an error to give diagnosis of exclusion the same epistemic weight as diagnosis from inclusion, which relies solely upon positive evidential findings.

Conclusion

Diagnosis of exclusion is commonly used in clinical practice; however, it is epistemically problematic. In this paper I argue that positive evidence for a disease or disorder is the only sort of evidence that counts toward an epistemically viable medical diagnosis. Thus, diagnosis from exclusion, although useful in clinical practice, does not have the same epistemic standing as diagnosis from inclusion.

References

Li, John C. (2013) Ménière's Disease: www.emedicine.com/ent/TOPIIC232.htm

Pellegrino and Thomasma (1981). A Philosophical Basis of Medical Practice Oxford: Oxford University Press.

[1] Pellegrino and Thomasma p. 128

[2] Li (2013)

[3] Ibid.

Using integrated history and philosophy to inform diagnostic medicine: the case of heart failure

Nicholas Binney, University of Exeter

There is a significant body of philosophical literature available which explores evidence-based medicine and the justification of therapeutic interventions. However, it may be the case that much less philosophical attention has been paid to the justification of diagnostic practices. I would like to argue that integrated historical and philosophical research can be used both to understand how physicians attempt to justify their diagnostic practices and to inform diagnostic medicine itself. As such, I

question the autonomy of the philosophy of diagnosis from the philosophy of other forms of measurement and classification. To do this I take as a case study of the disease 'heart failure'.

Many cardiologists today express their concerns over how physicians in general practice (GPs) diagnose heart failure. These cardiologists argue that GPs rely on clinical signs and symptoms to make a diagnosis of heart failure, and that using clinical signs and symptoms alone is inaccurate for this purpose. The European Society of Cardiology (the ESC) is a prominent, pan-European society of cardiologists who make this argument explicitly in their published guidelines on the diagnosis of heart failure. I will review the ESC's argument, and show how it is problematic. I will then present an historical overview of how the diagnosis of heart failure has developed over the last two hundred years and use this to show how philosophical assumptions made by physicians lead to these problematic arguments. I will suggest how integrated historical and philosophical work might be used to inform diagnostic medicine itself.

The ESC argue that because clinical symptoms and signs are not accurate when used alone, echocardiographic evidence of cardiac dysfunction must be demonstrated for an accurate diagnosis of heart failure to be made. To make this argument, they appeal to research which measures the diagnostic accuracy of clinical signs and symptoms. Such measurements are made by seeing whether the results of a diagnosis made using symptoms and signs alone are in agreement with the results of a diagnosis made using some other highly trusted method of diagnosis (the 'reference standard'). I will argue that the ESC's choice of reference standards is problematic.

The ESC uses two different sorts of reference standard to measure the diagnostic accuracy of clinical symptoms and signs. On the one hand, they use reference standards which they themselves argue are inaccurate in their diagnostic guidelines. I argue that the ESC should consider any evidence produced in this way as untrustworthy, and that their use of such evidence in their arguments is problematic. On the other hand, they also use reference standards which require both the presence of the appropriate symptoms and signs and echocardiographic evidence of cardiac dysfunction. This means that the ESC argue that echocardiographic evidence of cardiac dysfunction is necessary for an accurate diagnosis to be made because clinical symptoms and signs are inaccurate when used alone, and that clinical symptoms and signs are inaccurate when used alone because echocardiographic evidence of cardiac dysfunction is required for an accurate diagnosis to be made. I argue that this argument is circular, and that the ESC's use of it is therefore problematic.

I also identify a number of important contradictions in the ESC's diagnostic guidelines. For example, In addition to arguing that both the appropriate symptoms and signs and echocardiographic evidence of cardiac dysfunction are required for a diagnosis of heart failure to be made, the ESC also argue that heart failure is a diagnosis of exclusion. I argue that if heart failure is a diagnosis of exclusion, then it can be made without finding echocardiographic evidence of cardiac dysfunction. It is a contradiction for the ESC to claim that echocardiographic evidence of cardiac dysfunction is both necessary and unnecessary.

I will use my analysis of the ESC diagnostic guidelines to argue that many physicians make important philosophical assumptions with respect to the diagnosis of disease. Many physicians seem to make the ontological assumption that there is a single 'correct' method of diagnosis, which will classify patients optimally for any medical purpose. They also seem to make the epistemological assumptions that knowledge of what this method of diagnosis is is fully determined by the empirical evidence gathered about heart failure, and that this knowledge was produced in a cumulative process.

However, historical research which explores how the diagnosis of heart failure has developed can be used to show that these philosophical assumptions are problematic. I will present an overview of how the diagnosis of heart failure has developed over the last two hundred years and use it to show how these philosophical assumptions produce the problematic arguments and contradictions identified in the ESC diagnostic guidelines.

I will argue that the diagnosis of heart failure has developed in an iterative process, where one diagnostic method is rejected in favour of another logically incompatible diagnostic method. I will describe eight iterations through which the diagnosis of heart failure has developed from the early nineteenth century to the present day. This process has produced several logically incompatible diagnostic practices which select different groups of patients as diseased, several of which are potentially useful today in different medical contexts. I will argue that the contradictions identified are the result of physicians' attempts to present these different practices as part of a single 'correct' version of heart failure. I will also argue that the decision to reject one diagnostic method and accept another in each iteration was an historically contingent choice, and was not fully determined by the evidence available at the time. I will argue that the problematic arguments deployed by the ESC are the result of physicians' attempts to present the justification their current diagnostic practices not as the result of an iterative and historically contingent process, but as the result of a cumulative process which is fully determined by the available evidence. Overall I will argue that integrated historical and philosophical work can be used to inform diagnostic medicine.

Divided we stand; united we fall – the problems of particular patients in public health, epidemiology and health policy

CJ Blunt, Department of Philosophy, London School of Economics

We're familiar with the maxims 'United we stand; Divided we fall', and 'All for one; One for all'. In medicine, these make for particularly destructive practice—especially the policy of 'one for all'. Every practitioner knows that even superficially similar patients react very differently to the same treatment. Standardisation may spread out the costs and benefits—but it is, I will argue, clearly a suboptimal approach.

I argue for two theses—one obvious and uncontroversial, and a second with more bite. First, I argue that treating individuals by 'doing what's best on average' is a suboptimal approach. Medical practice should not subordinate patient care to the average treatment effect. In particular, the Evidence-Based Medicine movement has equated effectiveness with effectiveness on average. But clearly patient features significantly modify the effectiveness of a treatment, and estimates of average treatment effects omit crucial information about the variance and heterogeneity of a treatment's effect in the target population. Any statistician would realise the inadequacy of basing individual healthcare decisions upon the mean while neglecting the variance.

My second and more controversial thesis is that fields beyond individual patient care can and should learn from the problems of heterogeneous treatment effects. If clinical epidemiology is to inform patient care, then clearly a shift towards focus upon the information practicing clinicians need—namely information about the heterogeneity of treatment effects, and about the patient features which modify treatment effectiveness—is vital.

But clinical epidemiology is not the only area which must take account of the philosophical lessons from the flaws of the Evidence-Based Medicine programme. Fields which are specifically concerned with overall benefit and population-level policies should still take account of individual treatment effects. In public health, if we wish to institute a broad-based 'one for all' policy, then we must still take into account more than just the average. This thesis results from a few relatively innocuous assumptions about the goals of public health policy. Public health policy is not a simple matter of utility-maximisation. Rather, we are concerned both with improving the lot of the worst-off as a priority, and with a fair distribution of benefit across the affected population. Consider two policies to reduce the spread of an infectious disease, A and B, which have equal net effects on the incidence of the disease. 'A' brings about a small reduction in risk of the large proportion of the population already at low-risk of exposure. 'B' brings about a large reduction in risk to the small high-risk population.

Clearly, though the net effect is the same, 'B' is preferable given prioritarian and/or distributive justice concerns.

Moreover, health policy must take account of the variation in treatment effects across individual patients. For instance, the much-emulated NICE in the UK evaluates the cost-effectiveness of treatments through the ICER (Incremental Cost Effectiveness Ratio). However, the cost-effectiveness of a treatment as determined by NICE depends sensitively upon the population in whom we consider the effects. Suppose C is a costly treatment which is highly effective in a few high-risk groups, but much less effective in the majority of patients. If we evaluate the ICER of C in the whole target population, then C will seem to be cost-ineffective, and governmental or insurance bodies might decide not to compensate C-treatment. However, if considered only in the high-risk subpopulations, C will appear much more cost-effective. In reality, things will not be so simple—there are a range of variables which modify treatment-effectiveness. As such, 'united we fall'—lumping all patients in together provides unhelpful information about cost-effectiveness, leading to blunt-instrument suboptimal policies. Taking account of research into the heterogeneity of treatment effects and the causes of varying effectiveness will allow targeted assessment of treatment effectiveness and cost-effectiveness—'divided we stand'.

The concern over heterogeneous treatment effects is far from idle philosophical speculation. There is real and ever-mounting evidence that treatment effects are heterogeneous and modified by a number of dimensions. I explore four case-studies in particular. From the perspective of clinical epidemiology, the case of carotid endarterectomy is highly instructive—carotid endarterectomy is highly effective at reducing stroke-risk in patients with severe carotid artery stenosis, but may in fact increase stroke-risk in patients with moderate or asymptomatic stenosis.

With respect to health policy and public health, cases such as the Oprelvekin/Oprelvekin scandal, quinidine for atrial fibrillation, and temozolomide for glioblastoma are powerful examples. In the cases of Oprelvekin and quinidine, an identifiable subset of the population suffers severe side-effects or paradoxical effects (effects opposite to that intended). This led in both cases to the drugs being withdrawn—in Oprelvekin case, after a scandalising suppression of the accumulating evidence that the drug caused hepato-renal failure in the elderly. However, these cases illustrate the challenges for drug licensing and for the calculation of cost-effectiveness and treatment-effectiveness where heterogeneity of treatment effects predominates. In both cases, an efficacious drug was lost to us because of failure to take account of predictable individual variations and police prescription and policy accordingly.

In the case of temozolomide, an identifiable subset of the target population (those with inactive MGMT DNA-repair gene) are responsive to the chemotherapy. Again, average figures suggest a small benefit for this expensive treatment—an ICER calculation at the general level would suggest against compensating for this treatment. But things are very different when the independently identifiable population of high-responders is considered: in that population, the treatment may be worth the cost and side-effects.

The insights from philosophy of medicine and the EBM debate are pertinent and instructive for public health, health policy and epidemiology.

Session 2 – How history, sociology and ethics can influence epistemology of medical knowledge? Chair – Giovanni Boniolo

From classical medicine to molecular medicine – only a problem of methods?

Giovanni Boniolo, European Institute of Oncology, Department of Health Sciences, University of Milano

“Times they are a changing”, Bob Dylan was singing some years ago. We should take into account what this means, in general, for knowledge and, in particular, for medical knowledge. For, over the last five/six decades an enormous leap forwards in biomedical knowledge has been done, thanks to both the discoveries in the field of molecular biology and the amazing biotechnological innovations. Thus, it is almost a shared platitude to assert that we are facing a new era in medicine. Nevertheless it seems not so shared the idea that we need to pause and reflect on what is happening in order to grasp whether we are spectators of a really new manner of practicing medicine, that is, whether *molecular medicine* and *personalized medicine* truly involve novelties.

This means inquiring the foundations of this two “approaches”, also to understand which the relationship between them is. Yet, it should be a historically-driven inquiry: it is impossible to grasp the novelties of a human product without considering the historical background in which it was incubated and from which it departs.

However, after Popper’s lesson, according to which “we are not students of some subject matter but students of problems”, I will not look for the “essential” features of molecular medicine and personalized medicine: a task which could be useless and frustrating. Disciplines are historical and social constructions produced mainly for academic scopes. I accept Popper’s suggestion and I could look for problems. Actually, this should be an easy task. It is almost totally shared that while the core problem of molecular medicine consists in understanding the molecular basis of the pathologies and, thus, in how to prevent and possibly cure them with our molecular knowledge, the main problem of personalized medicine should be individuated in the actualization of a preventive, diagnostic and therapeutic path focused on a patient, thought of as an individual with his/her own genome, his/her own life style, his/her own living environment, his/her own biological and non-biological biography.

Unfortunately, differently from Popper, I do not think that this could be enough. Even if the two problem-based definitions above could be accepted, they would not give us what molecular medicine and personalized medicine are, in particular would not satisfy our intellectual need to understand whether, and in which sense, they represent a real improvement in medical knowledge. Claiming that now we know more on pathologies since we know more from the molecular perspective is not sufficient to assess the effective step forward that is voiced to be. That is, molecular medicine and personalized medicine are not a drastic change in our thinking and practicing medicine only because of the molecular level of their analysis. There should be something more and, as I suggest, this is in the method.

Alternative experimental philosophy meets philosophy of medicine: where sociology has never been before

Stéphanie Van Droogenbroeck, Vrije Universiteit Brussel

In the first part of this paper we will analyze the general idea of experimental philosophy. By broadening this concept it will become clear that EP may be useful for the philosophy of medicine. The second part concerns the distinction between a broadened –or alternative- EP and sociology. We

will show that even by using a methodology from sociology, it still is not sociology, but rather philosophy. An example of ongoing research will clarify these statements. A study in two Belgian hospitals on medical diagnostics focuses on uncertainty, the use of evidence based medicine (EBM) and tacit knowledge. Ethnographic research is performed: which is a qualitative methodology originated from sociology. We will discuss some results of this study in order to demonstrate (1°) the avail of alternative EP, and (2°) the difference of alternative EP with respect to medical sociology.

1° Experimental philosophy (EP) tries to understand the intuitions of all kinds of people on philosophical subjects. Experimental philosophers use quantitative methodologies from the cognitive sciences instead of doing armchair philosophy. There has been a lot of justified and unjustified critique on this methodology. (e.g. Knobe and Nichols 2008) But one major critique on EP touches the core of philosophy. Kauppinen states that the intuitions are being “tested through the methods of non-participatory social science [...]. At best- survey results provide food for thought- but we are better nourished if instead of designing artificial setup we pay close attention to what is said in real life situations of language use, as conscientious philosophers have done at least since Socrates.” (Kauppinen 2007)

We can solve this problem by using a qualitative methodology as this implies a non-artificial setup. We can call this alternative EP. Alternative EP –like EP itself- tries to understand the intuitions of people on philosophical subjects.

Some examples from the Belgian study will be given and it will be demonstrated that the use of an ethnographic methodology is more suitable for this research problems than a survey method which is commonly used in EP. Ethnographic research leads to high external validity. This gives new insights into the situation and intuitions. Besides this advantage we will discuss some other features of ethnography in order to show its benefits for philosophical research questions.

2° EP and alternative EP use methodologies from sociology. Whereas EP focuses on survey methods, alternative EP uses qualitative methodologies. These are both still philosophy because of the goal of the research. Sociology wants to get a better grip on society and its problems. Sociologists do this from their own framework and view on the world. And philosophers want to get a better grip on society by looking through their own philosophical glasses. These glasses color society and lead to specific philosophical problems such as the problem of demarcation and the problem of induction that states that induction cannot be justified by deduction.

To make this argumentation more concrete, we will demonstrate this with by describing some cases from the study: Although most physicians claim to perform EBM and sometimes ignore and other times acknowledge the use of tacit knowledge, they use tacit knowledge more than they admit. Tacit knowledge plays an important role in medical practice. This is in contrast to the intuitions of some people concerning EBM. (Goldenberg 2006) This use of tacit knowledge seems to help physicians and patients to get a better understanding of the situation. It is also a way of dealing with the amount of uncertainty in a clinical setting. As we will show- this idea has some implications for the demarcation problem; which is a philosophical issue.

In other words, the difference of this philosophical research in relation to medical sociology is that we start from a philosophical question such as what is EBM in the light of epistemology and then continue with a field study- preferably a qualitative study as a starting point in such complex issues like intuitions on EBM. These results of the field study are analyzed and discussed with philosophical literature on EBM, uncertainty and tacit knowledge. In medical sociology we start from a sociological problem such as medicalization in diagnostics (e.g. Jutel 2007), then we use a quantitative or qualitative methodology. We end by analyzing and discussing the results from sociological literature and by using sociological jargon. This kind of research does not give any answers to a specific philosophical problem such as the justification of philosophers their view on EBM or the demarcation problem.

Thus, both sociology and philosophy try to explain phenomena but they both do it with their own colored glasses. This makes us conclude that even if philosophers make use of sociological methodologies, it still is philosophy.

Goldenberg, M.J. On evidence and evidence-based medicine: Lessons from the philosophy of science, *Social Science and Medicine*, 62, 2006, pp. 2621-2632.

Jutel, A. 2007. Sociology of Diagnosis: A Preliminary Review, In: *Sociology of Diagnosis (Advances in Medical Sociology, Volume 12)*, ed. PJ McGann, David J. Hutson. Emerald Group Publishing Limited: 3-32.

Kauppinen, A. 2007. The Rise and Fall of Experimental Philosophy. *Philosophical Explorations* 10,no.2: 95-118.

Knobe, J., and Nichols, S. 2008. An Experimental Philosophy Manifesto. In: *Experimental Philosophy*, ed. J. Knobe and S. Nichols. Oxford: Oxford University Press: 3-16.

Analysis of the concept of « intrauterine patient »: history, ethics and epistemology at the crossroads

Hélène Richard, Institut d'Histoire et de Philosophie des Sciences et des Techniques

In this paper, we first examine how the concept of "intrauterine patient" has historically been coined. Secondly we analyze the properties that conferred the status of patient to the fetus. We finally oppose this historically and technologically constructed concept to the paradigmatic vision of the patient as a suffering person in demand for care. This comparison will enable us to balance two visions of the patient: one resulting from the analysis of biomedical texts and clinical practice, the other from an ethical reflection on what the patient should be, based on a set of rights and moral conditions.

In the first part of our paper, we will present the unknown history of fetal medicine and the emergence of the concept of intrauterine patient. Analysis of medical texts (obstetricians handbooks since the early nineteenth century and systematic analysis of the French journal *Gynécologie et Obstétrique* since 1874) allows us to challenge the common misconception that the techniques of prenatal diagnosis and fetal medicine were developed in the 1960s. Indeed, the concept of fetal medicine emerged in the early nineteenth century, when Alexandre Lejumeau de Kergaradec wrote in his *Mémoire sur l'auscultation appliquée à l'étude de la grossesse* (1822), that it would be possible from now to focus on the "state of health and disease" of the fetus. The techniques of prenatal diagnosis were developed during the nineteenth and twentieth century, with the development of fetal auscultation, the introduction of biochemical analyzes, the use of radiography throughout the first half of the twentieth century, the introduction of fetal karyotype in the 1960s, the emergence of ultrasound and finally with the analysis of fetal genome. However, clinical interventions were extremely limited until the middle of the twentieth century: risky treatments in cases of infectious diseases, therapeutic abortion in case of diagnosis of "fetal monstrosity" (although it did not fall within the public sphere before its legalization in 1975), termination of pregnancy to treat *ex utero* premature infants, especially in the case of erythroblastosis. The treatment *in utero* of erythroblastosis will introduce the term of intrauterine patient. Erythroblastosis fetalis is a disease in which the Rh negative pregnant woman immunizes herself against the paternally inherited Rh positive antigens carried by red blood cells of the fetus. The antibodies produced by the mother pass through the placenta and enter the fetal circulation to cause the destruction of red blood cells. Liley, the "patron saint" of fetal medicine, carried out the first intrauterine transfusion in 1963. Commenting on the symposium "Diagnosis and treatment of fetal disorders" of 1967, Claude Sureau talked about the new accessibility of the intrauterine patient: "diagnostic accessibility" and "therapeutic accessibility" (*Gynécologie et Obstétrique*, 1970). The term of "intrauterine patient" has then spread within the medical community and fetal medicines as a well-established subdiscipline progressively find its proper place within hospitals.

In the second part of our presentation, we will review the properties that conferred the fetus the status of patient by conducting a semantic analysis of biomedical texts and clinical practice. Historical reconstruction of this concept brings out four properties that were necessary for the fetus to gradually reach this status: 1. being presented to a physician (auscultation of the fetal heart marks the emergence of fetal medicine: it was possible to determine *in utero* whether or not the fetus is alive), 2. being the subject of diagnosis (radiography allowed the first *in utero* diagnosis of malformations, and therefore the first abortion in cases of serious and incurable diseases), 3. possessing an individual singularity that does not need to be a legal or a biological individuality (ultrasound confers its own singularity to the fetus and fits it into a set of relationships between practitioners, parents and society) and 4. being enrolled in a therapeutic relationship (fetal surgery, antiviral treatments, IVF with donor of mitochondrial DNA). All these properties were acquired by both the introduction of new techniques in the field of clinical practice and a distinction between several cognitive and semantic biological entities (Duden, 1993; Zerubavel, 1993).

In the third part of our paper, we will oppose these properties to the paradigmatic vision of the patient, as it has traditionally been dealt with bioethics literature (eg Baertschi, 1995; Engelhardt, 1996; Fagot-Largeault and Parseval, 1987; Singer, 1993; Tooley, 1983). In bioethics, two principles are central to the debate about the status of the fetus: the notion of person and the notion of beneficence. Bioethical reflection questions the “fetus as a patient” legitimacy both according to moral obligations owed to the fetus (should it be considered a person or not? in other words the question of fetal ontologies) and the suffering of the unborn child (principles of beneficence or maleficence). Bioethics analysis of the concept of the intrauterine patient thus focuses on two competing values: on the one hand, the autonomy of the pregnant woman and on the other hand, the principle of beneficence to the unborn child that is underpinned by the analysis of fetal ontologies. And yet we will show that these two main features of the paradigmatic figure of the patient are missing from the properties that conferred the fetus a status of patient. Neither the supremacy of suffering as a call for clinical practice (prenatal diagnosis could follow a screening health policy) and nor the notion of person (the “fetus as patient” does not require prior consent in clinical practice on fetal ontologies (Chervenak, McCullough, 2003)) have been taken into account in the factual emergence of the notion of « intrauterine patient ».

Finally, we will draw some conclusions from this major difference between analytical and historical reconstruction on the one hand and ethical questioning on the other hand, moving from the normative analysis of the concept of patient specific to the bioethics analysis to the co-production of norms inherent to the clinical practice (Foucault, 1963, 1969) and the use of techniques.

Baertschi Bernard, 1995, *La valeur de la vie humaine et l'intégrité de la personne*, Presses Universitaires de France.

Chervenak, Mc Cullough, 2003, « The Fetus as a Patient: An Essential Concept for the Ethics of Perinatal Medicine », *American Journal of Perinatology*, vol. 20, n° 8, p. 399-404.

Duden Barbara, 1993, *Disembodying Women: Perspectives on Pregnancy and the Unborn*, Harvard University Press.

Engelhardt H. Tristram, 1996, *The Foundations of Bioethics*, 2^e éd. Oxford University Press, USA.

Fagot-Largeault Anne et Parseval Geneviève Delaisi De, 1987, « Les Droits de l'Embryon (Fœtus) Humain, Et la Notion de Personne Humaine Potentielle », *Revue de Métaphysique Et de Morale*, vol. 92, n° 3, p. 361-385.

Foucault Michel, 1969, *L'archéologie du savoir*, Gallimard.

Foucault Michel, 1963, *Naissance de la clinique*, Presses Universitaires de France - PUF.

Kergaradec Jean Alexandre Le Jumeau de, 1822, *Mémoire sur l'auscultation appliquée à l'étude de la grossesse, ou, Recherches sur deux nouveaux signes propres à faire reconnaître plusieurs circonstances de l'état de gestation*, Paris, France, Méquignon-Marvis.

Singer Peter, 1993, *Practical Ethics*, Cambridge University Press.

Sureau, C., 1970, compte rendu de "Diagnosis and Treatment of fetal disorders", Adamsons, K., Symposium de Porto-Rico, 29-31 octobre 1967, Bulletin de la Fédération des Sociétés de gynécologie et d'Obstétrique de Langue Française, supplément e Gynécologie et Obstétrique, Tome 22, n°3, p.389.

Tooley Michael, 1983, *Abortion and infanticide*, Clarendon Press.

Zerubavel Eviatar, 1993, «In the Beginning: Notes on the Social Construction of Historical Discontinuity », *Sociological Inquiry*, vol. 63, n° 4, p. 457–459.

Adults seeking prescriptions for cognitive stimulants under the rubric of ADHD: a case study in the ‘unity and autonomy’ of Philosophy of Medicine within the Medical Humanities

Silvia Camporesi, King's College London (Center for the Humanities and Health)

As I am completing my PhD in Philosophy of Medicine at King's College London, but being based at the interdisciplinary Wellcome Trust funded Centre for the Health & Humanities (<http://www.kcl.ac.uk/innovation/groups/chh/index.aspx>), in the last three years I have had many chances to reflect on how my research relates to research being conducted by other scholars within the Medical Humanities (e.g History of Medicine, English, Science & Technology Studies, Medical Anthropology, etc), and on what this relation can tell us about the role and autonomy of Philosophy of Medicine. Today I will present to you one problem I have been researching on, and reflect with you on the different approaches that can be used to analyse it, how they relate to each other, and what they can tell us about Philosophy of Medicine as a discipline. The case I will discuss with you is the increasingly widespread practice in the US to seek prescriptions for stimulants (i.e. Ritalin, Adderall) under the rubric of adult ADHD. This practice opens up a number of interesting issues in Philosophy of Medicine and cognate disciplines in the Medical Humanities. Among these:

- a) Concept of Health and Disease: Can adult ADHD be considered a ‘disease’?
- b) Therapy vs. Enhancement distinction: Can the prescription of stimulants in adults be considered a treatment, or should it instead be considered an enhancement? What implication does the distinction have in terms of, for one, reimbursement of medical costs in the insurance-based US system?
- c) Discussion of concept of ‘Normal’ vs ‘Abnormal’: What can be considered ‘normal’ human cognitive capacities?
- d) What constitutes medical evidence? What kind of ‘evidence’ is being used to infer the ‘cognitive enhancing effects’ of such stimulants?

In my paper (currently under review) I chose not to focus extensively on a) b) c), but to take as a premise that such stimulants constitute an enhancement, and focus on d), and the ethical and policy implications that a shift of the prescription of stimulants from a disease rubric to an enhancement model would bring. But, of course, different scholars could have chosen to prioritize other points of analysis. The strategy adopted in the paper involved the integration of different approaches: a historical approach to analyse precedents of enhancement requests accommodated within the scope of medicine, a conceptual philosophical analysis (i.e., can adult ADHD be considered a disease? Should the prescription of stimulants be considered therapy, or enhancement?), aided by the contribution of research ethics (how can medical and scientific research on enhancement be justified? How do the ‘classical’ criteria for the justification of clinical research translate to the justification of research ethics?), and of philosophy of mind (as I argued that self-deception is present in at least a subset of the adults who actively seek prescription for Ritalin and Adderall).

Other approaches within cognate disciplines in the Medical Humanities would also, or could also, have been possible for this case study: for example, the use of sociological analysis to perform interviews and gather data on how widespread the practice is, on what kind of individuals are seeking the prescriptions, what their motivations are, etc. Or again, the application of an anthropological approach to a US-based practice which is deeply intertwined with economic and social issues, would also/could have been possible and fruitful.

In my analysis I was particularly interested in reaching some normative conclusions, and I therefore argued that the current model of prescribing Ritalin and Adderall under the rubric of ADHD being

ethically problematic for several reasons (which I will describe in my presentation) lends support to a shift to an enhancement model, where individuals could instead get prescriptions for cognitive stimulants independently of a diagnosis of adult ADHD. I concluded opening up questions of justifiability of reimbursement, of the appropriate mode of governance and regulation for research on enhancements, and of the proper scope of medicine in relation to who should accommodate such requests (the doctor? another figure?).

Such an analysis, I think, could not have been carried out only with the input of a philosophical analysis of concepts, but it necessarily needed inputs from cognate disciplines within the Medical Humanities. In sum, what can this case study tell us about the main topic of this conference? Indeed, when I reflect on the 'unity and autonomy' of Philosophy of Medicine, I think about the way a philosophical analysis of concepts (e.g. health, disease, ability, disability, identity, embodiment, gender, etc.) can be integrated with a historical approach, sociological and anthropological data, and - what interests me most- a contextual, bottom-up ethical analysis of the justifiability of a practice, in order to reach a normative conclusion, which could inform policy. From my perspective as a multidisciplinary researcher in Philosophy of Medicine, I accept the discipline's autonomy from cognate disciplines within the Medical Humanities, as I think that addressing questions such whether adult ADHD can be considered a disease; whether prescriptions for cognitive stimulants should be considered therapy, or enhancement; what can be considered 'normal' human cognitive capacities etc., can be interesting and self-exhausting inquiries carried out only with philosophical methods. This said, I find that a reflection limited to a conceptual analysis is merely 'relatively interesting', while I find more interesting and poignant a philosophical analysis of concepts coupled to an analysis grounded in cognate disciplines within the Medical Humanities - and therefore carried out with different methods grounded in each discipline- which tries to reach answers to questions such as, 'Should we do this, or not?' or "Is it ethically permissible that xy occurs, or not?", or 'Why is such a practice present in society x, and not y?' etc.

With today's presentation I hope to have made this point visible to you too.

Session 3 – Can and should philosophy of medicine free itself from philosophy of biology? Chair – Maël Lemoine

Commensalism or mutualism: What is pathophysiology to physiology?

Maël Lemoine, University of Tours

“Physiology and pathology do not constitute two distinct sciences, but two branches of the same science”, Claude Bernard wrote. “Creating a theoretical separation of pathology from physiology” is not appropriate, S. Moghaddam-Taaheri (2011) echoed. What exactly are the relations between physiology and pathophysiology?

The first step in resolving this question is to distinguish physiology, the science of mechanisms in health and disease, and normophysiology, the science of mechanisms in health – pathophysiology being its counterpart in disease. In a trivial sense, pathophysiology is a part of physiology. The non-trivial question is therefore whether pathophysiological science is only an appendage to normophysiological science or a different, but related, ‘twin science’. This in turn subdivides into two questions:

- 1) *Is the knowledge of functions in the system’s normal behavior **necessary** to understand its pathological behavior?*
- 2) *Would a complete knowledge of the system’s normal behavior be **sufficient** for the knowledge of the system’s pathological behavior?*

The traditional answer to question (1) is that pathophysiology depends on normophysiology because *a)* it is necessary to know what are a system’s normal functions in order to understand what happens in diseases, *b)* explaining abnormal behaviors generally comes down to pointing out a few structural variations of the system, and *c)* as disease as well as health are described by mechanisms, the difference between the two possibly relies on nothing but values. In response to this traditional view it has recently been advocated that focusing on the sequence of events in diseases is more practical than focusing on the difference to normophysiology (Nervi 2010).

The traditional answer to question (2) is that a complete understanding of normal mechanisms would in theory be a sufficient condition for a complete knowledge of abnormal mechanisms. The main reasons have been that *a)* diseases often imply nothing but quantitative variations in the level of normal functions, and *b)* when they do not, they nevertheless abide by the same laws of nature that make predictions and explanations of healthy mechanisms and processes possible. To this view, I object that *a)* from a complete normophysiology, only a theoretical science of *possible* dysfunctions and diseases would follow, whereas what we are interested in is the *actual* domain of pathophysiology; *b)* this actual limited domain can, and should, give rise to certain systematization and theorization; and *c)* at least some dysfunctional mechanisms are dysfunctional *per se*, independently of any normative judgment, and belong to pathophysiology as paradigms.

To conclude, I will show that pathophysiology’s independence is both a crucial question for naturalism in the philosophy of medicine, and a crucial question for the independence of the philosophy of medical science from the philosophy of biology.

In what sense are the clinical concept of function and its philosophical rendering “specific”?

Barthelemy Durrive, Université Claude Bernard Lyon 1, École normale supérieure de Lyon

The benefits of pluralism make it important to preserve through our efforts at unity. Both in philosophy and in the medical sciences, diversity in the definitions and methods helps to achieve greater relevance – and yet any field of study is but a battlefield without any common ground for the debate to stand on.

Moreover: if the many practices forming “the philosophy of medical science” are somehow autonomous vis-à-vis both “philosophy in general” (or any school of thought in particular) and the specific medical science each reflects on, they have to feature (or so we will argue) a certain form of unity, which is not so much a least common multiple as a shared situation.

Rather than describing it in general terms, we will try to mark out such a situation through a developed example (debates over the paradoxical status of the “physiological viewpoint” involved in functional explanation) and eventually extrapolate an interpretation suggesting why this peculiar common point could offer a sufficient basis for intradisciplinary discussion to take place.

Epistemologists as well as biologists have long engaged in the controversy over how should organic functioning and behaviour be accounted for in a theoretical perspective. Their explanatory concern regards the conditions at which a truly objective use of the concept of function is possible. The “etiological conception” (Wright, 1973) and the “systemic conception” (Cummins, 1975) thus provide our mechanistic paradigm with two (compatible) explanations to how non-intentional phenomena may still rest upon an apparent purpose. Considering functions respectively as “effects selected through Evolution” and “causes integrated in a self-regulatory system”, both conceptions do manage to blend the physiological viewpoint (despite its specific mode of intelligibility) into the naturalistic model which solely meets our standards of an objective explanation.

Now: do philosophers of medical science consider this precise question from a somehow specific perspective? And why would they? We feel that the issue here concerns less the relationship between “philosophy of science” and “philosophy of medical science” than (more radically) the one philosophers assume between fundamental sciences and the medical sciences.

As this assumption directly implies a certain relationship between medical sciences and medical practice. If the former is only a matter of application (medical sciences thus being mere “applied sciences” as opposed to fundamental ones), how could the latter be anything else than another “application” (this is to say, a literal use of the results and methods that have been proven objective) deducing practice from theory?

Surely research in any medical science (neurophysiology, for instance) could make more use of evolutionary reasoning, enriching its organisational understanding of functions with an outlook on their historical dimension. But as far as the clinical is concerned – that part of the scientific inquiry supporting diagnosis, prognosis and therapy, thus dealing with individual cases –, are those two concepts (and associated viewpoints) relevant enough to be exhaustive and hence excluding of any other model?

To those two last questions (general and specific), our suggestion would be the following: philosophy of medical science is autonomous from general epistemology inasmuch as each medical science is from the fundamental science it rests upon. If clinical physiology had no need for a specific concept of

function, if it were simply applying those of biology, if there were no difference whatsoever between the laboratory phenomenon and the clinical reality – what would philosophers of medicine have to say that epistemologists wouldn't already know?

Regarding the “physiological viewpoint”, one could argue that both concepts discussed lack a decisive feature yet required in routine clinical analysis: the qualitative criterion by which functions are judged more or less satisfactory (and not only effective) on a multidimensional scale and on the basis of one's living experience. As this concept of a “normative” function is itself “normative” (as opposed to, but not incompatible with, an “objective” definition), it originates from a “normativist” conception of health (Nordenfelt, 2004) but the more to broaden the subject: the difference between “causal” and “normative functioning” becomes a decisive epistemological issue (Canguilhem, 1966, 125–150), whereas the emergence (or more broadly, the mode of existence) of normativity in a naturalistic ontology consisting only of “state of things” (Bickhard, 2003) regards the problems of biomedical ontologies.

However central the subject of normativity is, it would be far too simplistic to suggest it could serve as a “common point” constituting *de facto* “philosophy of medical science” into a united discipline. Actually we would like to suggest just the contrary: the paradoxical situation this “normative physiological viewpoint” is in towards fully objective scientific viewpoints constitutes both the specificity (that is: the autonomy) and the consequent unity of “the philosophy of medical science” (as well as of “the medical sciences” towards the fundamental ones). For if one part of “philosophy of medical science” did not share the paradox this “normativist epistemology” is in, the exception would break up any unity of the discipline, and we could suspect the many philosophies thus over-dependent on their peculiar science to not have any consistent autonomy.

Bickhard, Mark, 2003. Processes and Emergence: Normative Function and Representation. In Seibt, Johanna (ed.), 2003. *Process Theories: Crossdisciplinary Studies in Dynamic Categories*. (121–155), Dordrecht: Kluwer Academic.

Canguilhem, Georges, 1966. *The Normal and the Pathological*. Part Two: Do Sciences of the Normal and the Pathological Exist?, Chapter 2: A Critical Examination of Certain Concepts. (125–150), New York: Zone Books, 2007.

Cummins, Robert, 1975. Functional Analysis. *Journal of Philosophy* 72, 741–765.

Nordenfelt, Lennart, 2004. The Logic of Health Concepts. In Khushf, George (ed.), 2004. *Handbook of Bioethics: Taking Stock of the Field from a Philosophical Perspective*. (205–222), Dordrecht: Kluwer Academic.

Wright, Larry, 1976. Functions. *Philosophical Review* 82 (2), 139–168.

Rethinking the Biology-Medicine Relation via Phenotypic Flexibility and Robustness

Jonathan Sholl, KU Leuven

Since the advent of the Modern Synthesis in the early 20th century whereby the theory of natural selection and genetics were brought together, there have been many attempts to relate, describe or even ground medical concepts, such as health and disease, on biological phenomena (Canguilhem; Boorse; Nesse; Wakefield; Nordenfelt; etc.). While these attempts, further developed since the 1990s with Darwinian medicine (Nesse and Williams), have greatly contributed to an evolutionary explanation of the problem of ‘why we get sick’, they are not without critics who claim that the biological goals of survival and reproduction often run counter to medical goal of ensuring the health of the individual (Gammelgaard).

Furthermore, Darwinian medicine's stress on a certain kind of evolutionary thinking, adaptationism, which is the idea that traits are to be understood as products of optimized trade-offs that have been shaped by various selection pressures, as well as its reliance on past environments (particularly the

environment of evolutionary adaptedness, or EEA) to explain contemporary pathologies, have hindered attempts to develop a coherent account of health and disease (Stearns; Valles). While research into the developmental origins of diseases and mismatch theory provide more detailed accounts of disease etiology (Gluckman and Hanson), Darwinian medicine still struggles to incorporate individual-level adaptations to changing environments into its understanding of health and disease, thereby reducing health to the mere absence of disease, and disease to a disadvantageous deviation from (past) species norms.

The aim of this paper will be twofold. First, after briefly outlining the contributions and limitations of Darwinian medicine to defining health and disease, it will suggest that the phenomena of within-individual phenotypic plasticity and biological robustness could be harnessed to better define health and disease. As phenotypic plasticity can refer to the products of the interaction between genotypes and environments as well as morphological processes (Nicoglou), it operates on various biological levels, all of which help to clarify the origins of disease (Gluckman et al.). However, the phenomenon of reversible within-individual responses to environmental heterogeneity, or phenotypic flexibility (Piersma and Drent), brings us closest to the physiological concerns of medicine. The concept of robustness, whereby a system maintains a function amidst internal and external perturbations, also refers to various biological processes, but has proved useful for describing various diseases such as cancer and metabolic syndrome (Kitano). While robustness and flexibility refer to rather specific biological processes, their ubiquity throughout biological taxa and their ability to describe individual-level processes make them particularly helpful for addressing medical concerns without rejecting naturalist and evolutionary intuitions.

Furthermore, some insights by the philosopher of biomedicine, Georges Canguilhem, regarding the historical and individual nature of biological norms, and the impossibility to clearly separate organism and environment when defining health and disease, will be used to problematize appeals to past environments to explain current pathological states. Taken together, these insights will contribute to defining health as an individual-level capacity to tolerate environmental perturbations (robustness) and the ability to establish new norms in the face of varying environmental demands (flexibility). In this view, health is not merely normal functioning, but entails the surpassing of previous norms. Conversely, disease is not merely a deviation from (past) species norms, but the presence of a new norm entailing a weakened robustness and constrained flexibility within the current environment. As disease entails a novel relation between the individual and its environment, pathological processes cannot be deduced from normal functions. These definitions will aim to address the aforementioned problems that arise when evolutionary explanations are brought to bear on medical concerns.

Second, these definitions produce an interesting paradox. On the one hand, health and disease become biological phenomena describable in terms of individual-level processes, which are themselves a unique mix of genetic, phenotypic, developmental, behavioral, and ecological processes. These definitions can help to address the aforementioned antagonism between biology and medicine by giving due weight to the individual organism, rather than simply genes or groups, thereby bringing biological and medical goals together. On the other hand, these descriptions are not reducible to or derivable from biological analyses, as naturalistic accounts would suggest (health as normal functioning), precisely because they remain relative to the individual's contingent relation to its constructed environment (Lewontin; Odling-Smee et al.), which is thoroughly affected by historically (and culturally) changing conditions.

While clarified in terms of organism-level processes, it is still relative to the concrete individual in a particular environment as to whether such processes are considered healthy or pathological. As such, defining health and disease in terms of robustness and flexibility implies an environmental and individual relativity of these concepts. Thus, rather than signaling a definitive grounding or deduction of medical concepts from biological processes, these definitions will show that the very concepts of health and disease are a function of historically changing conditions, further stressing the complex relation between biology and medicine.

Symptoms in vivo and in vitro : Cellular reprogramming between biology and medicine

Pierre-Luc Germain, Università degli studi di Milano, European School of Molecular Medicine, European Institute of Oncology

Although there is no truly “pure” science, nowhere is the distinction between knowledge-seeking and -application as blurred as it is in medicine, leading to an intertwining of both epistemological and ethical issues which ought not (and, arguably, cannot) be analysed separately. Nevertheless, although philosophy of medicine used to also be a philosophy of biology, the current compartmentalization of scientific and philosophical sub-disciplines tends to treat problems of the lab independently of problems of the clinic. Paradoxically, perhaps the most persistent such division concerns precisely the so-called “translational medicine”: translation already implies a distinction between two systems, a directionality, and something there to be translated.

Even leading proponents of translational medicine, who repeatedly emphasize that translation is “a two-way road”, seem to have a surprisingly simplistic idea of this process: the lab provides predictions to be tested clinically, and the clinic at best provides raw materials in the form of *ex vivo* samples (see for instance the inaugural editorial of the *Journal of Translational Medicine*). The aim of my paper is to study the intricacies of the relationship between the lab and the clinic, and to argue against a dichotomous and polarized view of biomedical research. Such a study can provide insights not only regarding the process of biomedical research, but also the contemporary practice of both medicine and biology.

I rely on the particularly revealing example of disease modelling using induced pluripotent stem cells (iPSCs), a research programme which has recently received much attention following the award of the 2012 Nobel prize to J.B. Gurdon and S. Yamanka for cellular reprogramming. Because it allows the derivation, from a simple skin biopsy, of virtually any cell type of the same genotype, the reprogramming technology presents two unprecedented experimental opportunities: the study of human genetic variation, and the study of human tissues which used to be inaccessible, such as tissues from the central nervous system. In doing so, it also provides very concrete means of integrating patients' medical history into basic laboratory research. For this reason, it makes particularly obvious the many (and bidirectional) transactions between the bench and the bedside, extending much beyond the mere transfer of *ex vivo* materials. Concentrating on a specific aspect, I show how *in vivo* phenotypes (both clinical and from animal models) are extrapolated to the dish, leading to the establishment of cellular phenotypes – including cell and tissue identities and other biological “kinds” that can then be applied outside the medical context. This implies that an understanding of even fundamental experimental biology requires an understanding of its many links to medicine, and also suggests that Canguilhem's observation of the priority of the pathological still find echoes in contemporary research.

Extrapolation, whether from or to the dish, is fallible, and therefore cellular phenotypes associated to a disease are not necessarily causally relevant for it. For this reason, proponents of iPSC disease modelling acknowledge the complementarity of animal models, in which the pathological relevance of the *in vitro* will be tested. Importantly, however, extrapolation works both ways: *in vitro* phenotypes are themselves extrapolations of *in vivo* phenotypes, and their relevance is tested by verifying whether an *in vivo* correction of the *in vitro* phenotype also rescues the *in vivo* phenotype. On top of the target system (patients), this therefore involves more than one model, and as a consequence, the relation between either model and the target system cannot be understood independently of each other. In other words, the traditional understanding of biomedical models in terms of a dyadic relationship between a model and a target system is insufficient on two grounds: it leaves unanalysed the relationship between the two models, and fails to account for the interdependence of the two respective relations between the model systems and the target system. Instead, I argue that the target system is itself part of a distributed networks of models. These are inter-connected through material relationships (e.g. in

in vitro culture of tissues from a characterized animal, or in vivo transplantation of in vitro models) or through the mediation of abstract terms and entities which appear at the intersection between models.

The change of focus obtained by setting aside the dyadic model-to-target relationship also brings into light the extent of the patient's inscription into the activity of modelling. Critiques of iPSC modelling, moved by scientists' usage of medically loaded concepts in the context of the dish (“diseases-in-a-dish”, iPSC as “the new patient”, cellular phenotypes as “symptoms” to be cured, etc.), have complained that the programme would move the normative aspect of medicine to the lab. This old worry however obscures the opposite risk: namely of bringing the lab – now in its epistemic rather than technical form – into the clinic.

Fighting infectious diseases: how an ecological vision of disease may inform biomedical and therapeutical strategies?

Gladys Kostyrka, Institut d'Histoire et de Philosophie des Sciences et des Techniques

The last century has seen an important change in our understanding of infectious diseases. The conceptual framework progressively shifted from a reductionist to a more integrative approach. Identification of the molecular properties of the infectious agent and description of the physicochemical mechanisms of the associated disease were no more sufficient to understand, prevent and treat the disease: biomedical researchers had to also pay attention to the ecology of disease (Theobald Smith 1934, Frank Macfarlane Burnet 1940, René Dubos 1965, Warwick Anderson 2004). “Disease ecology” covers a great number of past and present practices, but, common to all these practices is the refusal to reduce the cause of disease to its microbial agent: an infectious disease can't be simply understood and treated by tracking the infectious microbe and understanding its molecular properties. “The forces and conditions controlling disease are a mixture of heredity, environment and parasitism” (Theobald Smith 1921). “Microbe hunting” and the study of physicochemical mechanisms of disease are only a small part of the job. Biomedical research on infectious diseases must integrate an ecological perspective, insisting on the role played by the biological milieu in which the couple host-microbe is embedded: identifying the global network of biological interactions in a given milieu may lead to a better understanding of why and how an infectious disease appears and develops.

Along these lines, an “ecological style of reasoning” emerged. Although it was first separated from the “molecular style of reasoning”, it started to form bridges, sometimes complex, with it from the mid-1990s (Pierre-Olivier Méthot 2011). Yet the impact of such an ecological perspective on biomedical and therapeutical strategies may not always be obvious and remains doubtful in some cases. Traditionally, strategies used to fight against infectious diseases rely on the “molecular style”, trying to understand the pathogen, its life cycle and molecular properties, in order to destroy or inhibit it. Antibiotics for instance are built to specifically destroy some bacteria by acting on the physicochemical properties of the bacteria. Do the ecological perspective on infectious diseases either modify these “molecular” strategies or give birth to new strategies? To investigate this, I concentrate on the particular case of viral diseases, where most of the biomedical and therapeutical strategies, such as antiviral therapies or vaccines, seem to be almost exclusively centered on the molecular properties of the virus and on the physicochemical mechanisms of the associated disease. But does this analysis resist close scrutiny? In this paper, I show that it doesn't. Hence the question: to what extent can we say that an ecological perspective has informed and still inform the design of biomedical and therapeutical strategies in today's biomedical virology? Here I demonstrate that, in biomedical virology, the molecular design of strategies remains important, but it would be wrong to deny the influence of ecological preoccupations. I distinguish between biomedical strategies and therapeutical strategies to show that both are, but in different ways, concretely informed by ecology of disease.

I first define the concept of “strategy” in the context of viral biomedical research. This concept implies taking decisions on the means to employ against viral diseases (theoretical framework, explanatory

models, methods and techniques) ; but it also requires to precise the end to which a strategy must be used. “Prevention”, “recovering health” may be one of the possible ends. “Recovering health” used to be synonymous with the eradication of the infectious agent and the “restitutio ad integrum” (Boorse 1977). Yet inside a more ecological framework, the very concept of “health” is no more synonymous with the absence of microbes; and the end of the strategy tends to move from eradication to restoration of equilibrium. This conceptual transformation partly characterizes a “new epidemiology”, that coexist with a more traditional epidemiology , based on eradication and the idea that strategy is a countermeasure against the infectious agent (Andrew Mendelsohn 1999). This leads to the hypothesis that ecology influenced the ultimate goal of therapeutical strategies, moving it from “eradicating the microbe” to “restoring the biological equilibrium inside (and outside) the host”.

But I want to go further, distinguishing between therapeutical strategies and biomedical strategies, in order to properly evaluate the impact of an ecological perspective on each of these two categories. “Therapeutical strategies” refer to the different tools built to prevent, treat or attenuate a viral disease. These tools go from vaccines, antiviral therapies and drugs, to hygiene measures. By “biomedical strategies”, I mean the methods and techniques used to understand viral strategies and the way to interfere with their success. Medical virologists distinguish between a “blind approach”, where a great set of molecules are successively tested on a previously prepared infected culture, and a “cognitive approach” (Noël Tordo, 2012, unpublished interview), where each step of the virus reproductive cycle is analyzed to find the best way and moment to interfere with it. Therapeutical strategies, like biomedical strategies, seem to be centered on the molecular details of the infection process. This would lead to the conclusion that strategies in viral biomedical research are still deeply influenced by the “molecular style of reasoning”. And yet I demonstrate that the ecological style is also present, inside these strategies, under the form of always renewed hygiene measures, metagenomic studies, ethological research, or studies on apathogenic vectors.

Measuring the impact of an ecological vision in today's biomedical and therapeutical strategies will shed some light on the complex relations that today's biomedical research in virology entertain with its history and tradition: how is the ecological tradition in virology represented in today's biomedical research? Moreover, this case study requires to articulate a variety of research fields that often remain separated in the philosophy of medical science, such as epidemiology, biomedical ontologies and medical explanations. Finally, this investigation may contribute to a better understanding of the specificity of explanations in biology and in medicine, and how both could be articulated.

Pathology in context – response to Kingma

Lydia du Bois, University of Wisconsin Madison

Daniel Hausman offers a formulation of Christopher Boorse's bio-statistical theory of health. A similar naturalistic account of health and pathology has also been defended by Jerome Wakefield. Boorse takes it that the goals of organisms are survival and reproduction and that, “There is a pathology when the functional efficiency of a part is statistically subnormal in a reference class of an organism in a relevant environment.” (Hausman, forthcoming) The Boorse/Wakefield/Hausman (BWH) account has much to recommend it, if one is looking for an account of health that is value-free. However, Elselijn Kingma has raised objections (Kingma, unpublished manuscript) to the view – in particular Hausman's version of it – to which I respond by offering a reformulation of the BWH account. The objection in question claims that even the most sophisticated formulation of the bio-statistical theory is committed to misclassifying some conditions, such as those accompanying pregnancy as pathological. I will show that when assessing an individual's health with respect to a particular subsystem, relativizing the functioning of that sub-system to the functioning of other relevant subsystems will help avoid this and other the objections to the BWH account.

As it stands, the BWH account determines whether the functioning of one subsystem is pathological relative to the functioning of the system to whose goals the subsystem contributes. But the BWH

account fails to analyze pathology holistically. In the interests of providing a conceptual analysis of pathology that is not only philosophically water tight, but also applicable in medical contexts, it is important to offer a holistic analysis.

In complex organisms only rarely is just one subsystem dysfunctional. Much more likely is that at any time, two or more subsystems will be dysfunctional, leading together to the diseased state of the organism as a whole. While in some cases the dysfunctions of separate subsystems will be independent of one another, dysfunctions often interact, leading to a complex type of dysfunction. It is this combined complex dysfunction with respect to which the organism as a whole is then diseased.

Additionally, as the BWH account recognizes, there is significant variation in the functioning of parts and processes. There can be a wide range of functions such as muscular strength, diastolic blood pressure, etc. within the range considered healthy. The interaction of a particular level of functioning of one part or process with the levels of functioning of other parts and processes (rather than the functioning of the individual part or process by itself) determines whether there is a pathology.

The BWH account holds that whether or not an organism suffers from a pathology is assessed in part relative to its environment. By this is meant the environment external to the organism as a whole. Relativizing part function to the external environment is insufficient. The pathology of an organism as a whole also depends on a subsystem's functioning relative to the other subsystems of the organism and their interactions. In a sense, the functioning of parts and processes is relative to both the internal environment and the external environment.

Here is a sketch of how I propose to conceptualize pathology:

There is a pathology when the functional efficiency of a sub-system is appreciably worse than what is statistically subnormal relative to:

The reference class.

The external environment.

The functioning of the other subsystems of the organism.

Consider now Kingma's pregnancy objection: She argues that the current BWH account has to consider compromised pelvic floor muscles during the later stages of pregnancy as a pathology, because, relative to the reference class of women of childbearing age, the functioning of compromised pelvic floor muscles is statistically subnormal. However, if we isolate the purported pathology – that of compromised pelvic floor muscles – and include in our analysis the pelvic floor muscles' interactions with relevantly related subsystems, then the (non-pathological) functioning of the uterus explains the functioning of the pelvic floor muscles. The state of the uterus in a pregnant woman is obviously not pathological, because it contributes directly to one of the goals of the individual, namely reproduction. Thus, in the case of pregnancy, associated purported maladies are not in fact pathologies, since they can be explained by their being caused by changes in the reproductive system which are themselves not pathological.

This is contrasted with cases where Kingma maintains that, in trying to avoid the problems posed by the pregnancy objection, the BWH account mistakenly implies that the statistically normal response to an external environmental cause, such as a pathogen, is healthy. Liver failure caused by an overdose of paracetamol is statistically normal when relativized to the cause of the malady, but it is not healthy. Hausman responds to this objection by arguing that failed livers are not disposed to respond in a statistically normal way in many environments. But by that test, compromised pelvic floor muscles in pregnant women would apparently count as pathological, too. On the holistic account offered above, if we isolate the purported pathology – that of liver failure – and include in our analysis the liver's interactions with the environment, then we see that the idiosyncratic environment the organism finds itself in is not benign. Thus an inhospitable environment that contains a pathogen explains the functioning of the liver. The functional efficiency of a failing liver following poisoning is statistically subnormal relative to its reference class, is not a result of the healthy functioning of some other

subsystem, and is the result of an environmental factor which causes statistically subnormal functioning.

Treating the body as part of the environment in which a given subsystem is found then allows us to have a more accurate and informative account of pathology, which is naturalistic, and yet avoids the problems posed for the BWH account by Kingma.

Hausman, D. (forthcoming) "Health and Functional Efficiency"

Kingma, E. (unpublished manuscript) "Situation-Specific Disease and Dispositional Function: Response to Hausman"

Session 4 – Which methodological approaches for philosophy of psychiatry? Chair – Derek Bolton

Conceptualizing the medical gaze: definitions of disorder in and out the main psychiatry texts

Derek Bolton, King's College London

It is curious that the Director of the US main mental health research institute blogged apparently critical remarks of the new edition of the DSM, to be appropriated by an anti-psychiatry revival, on the same occasion, followed by a damage limitation joint statement with the incoming President of the Manual's owner, the APA. So how did NIMH get involved? In English we have the expression that 'the tail is wagging the dog'. In this case, the dog is the psychiatric nosology that we are all familiar with, and the tail is the pursuit of biomarkers. The usual way of seeing the absence of linkage between mental disorders and biomarkers looks like this:

There are no biomarkers for mental disorders (ICD/DSM Major Depression, Schizophrenia, etc.)

→ that's bad news for the biomarking paradigm (for 'biological' psychiatry; for psychiatry as a branch of medicine)

But the new way is like this:

There are no biomarkers for mental disorders (ICD/DSM Major Depression, Schizophrenia, etc.)

→ that's bad news for mental disorders – that is, as defined by the DSM/ICD.

Something had to give: either what NIMH stands for, or what DSM/APA stands for. Hard choice.

Psychologists are also involved: the American Psychological Association Humanistic Psychology Division (and 12 other divisions) and the British Psychological Society Clinical Psychology Division. A broad range of concerns about the DSM-5 have been expressed by these bodies, but of particular interest to the present topic they include the charge it is too medical, too biological, and ignores the whole person and their social context. The psychologists preferred alternative to diagnosis is 'formulation' which is more holistic and individualised and which would give due emphasis to psychosocial factors.

In some ways the Psychologists' complaint is the converse of Tom Insel's: the one is that the DSM is not enough biological, the other is that it is too biological and not enough psychological or psychological and social. So where does the DSM-5 really stand on these issues?

In this presentation I will review the current criticisms of the DSM-5 of the above sort, and go on to argue that the conceptualisation of mental disorder in the psychiatric manuals typically tracks personal, inter-personal and social phenomenology. On this particular issue I do not see much rationale for the complaints of the psychologists. The concerns of the biological psychiatrists – if this is the right term – seem to me more warranted. Biomarkers simply have no role in the DSM – or ICD – as in the earlier point. However, matters are not so clear cut because actually the RDoC are quite psychosocial too. The RDoC framework has a matrix in which there are columns labelled: genetic, molecular, cellular, neural circuitry, individual, family environment, and social context; in the rows there are conditions, which may be diagnostic or trans-diagnostic. There is no sense however that all these levels of analysis will always have causal relevance related to potential for intervention, let alone be equally important, regardless what conditions of interest are entered in the rows. Depending on the condition, genetic risk may be more or less important, for example, as may be the potential for psychological therapy to make any sustainable difference to the primary problem, or the causal role of social factors and potential for effective intervention in this domain. To make the point at one extreme: some conditions that might go into the rows of the RDoC framework will have no ticks under any

boxes indicating causal processes at levels other than e.g. the genetic or the neural, such as Huntington's disease, or concussion, i.e. no psychological or social factors make any difference – though they may do if the row had “adjustment to”. That is to say, reductionism to a single cause might be right in some cases and is in some cases already known to be right; in other cases the psychosocial might be more important, account for more of the variance in incidence or outcomes, than e.g. genetic factors. The new sciences for which RDoC provides a framework make discriminations between conditions in these respects, and in this sense the RDoC framework may be described as ‘biopsychosocial’.

Psychiatric objects in research and practice: Introducing the RDoC

Kathryn Tabb, University of Pittsburgh

Criticisms of psychiatry often focus on the hegemony of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* over not only diagnostics but also psychiatric research and treatment. Detractors have claimed that the *DSM* has maximized reliability at the cost of validity; that it has led to the pathologization of normal fluctuations in human experience; and that it has reified historically contingent psychiatric constructs at the expense of locating “natural kinds” of mental disorder. The first significant positive suggestion for a way forward (and away from the *DSM*) has been introduced by the United States' National Institute for Mental Health (NIMH). The NIMH's Research Domain Criteria (RDoC) project offers a new way to classify psychiatric research proposals that allows for researchers to identify their work in a matrix that lays out the potential research space for psychiatry. The rows on the matrix represent specific dimensions of behavior, called “constructs,” which are grouped together into domains of functioning. An example would be the domain of “positive valence systems,” which includes the constructs of “reward learning” and “habit.” An investigator interested in the role of salience acquisition and in psychopathology could propose research to the NIMH on this topic without framing her work as targeting, say, substance addiction or schizophrenia. The columns of the matrix represent units of analysis, ranging from genes up to self-reports. The NIMH's intention is that the progress of psychiatric research will no longer be hindered by the futile search for the putative mechanisms upholding the categorical boundaries codified in the *DSM*. It is important to note, however, that the RDoC is not intended to replace the *DSM* in clinical settings, nor is it intended to supply a new taxonomic structure for psychiatric kinds.

After presenting the RDoC and explaining how it dissents from the traditional approach to psychiatric nosology embodied by the *DSM*, I will make some remarks about how the advent of the RDoC should impact philosophical characterizations of psychiatry. Some philosophers have maintained that psychiatry should ultimately be considered a branch of applied neuroscience. I take the example of Dominic Murphy, who has argued that by focusing on causal explanations that emerge from cognitive neuroscientific research, psychiatry can become an objective science. The RDoC can be seen as a validation of this analysis by psychiatrists themselves. Murphy's work anticipated the shift towards a causal explanatory methodology that the NIMH is advocating, and much of his analysis is useful. In particular, he emphasizes that models of psychiatric disorder should be multi-level, and that few explanations in psychiatry will end up being “fundamental” — most will have only partial explanatory power given the messy complexity of their objects. He has introduced the notion of *exemplars* to describe concepts representing disease entities that act as the targets of psychiatric explanations, or *models*.

I argue, however, that Murphy overstates the potential for neuroscientific research to discover biologically-grounded psychopathological entities. Instead, I argue that the RDoC suggests a more modest target for psychiatric research: the explanation of mechanisms that cause signs and symptoms. Due to the outstanding complexity of the constitution of mental phenomena in the brain, the psychological level of explanation of psychopathology may be irreducible. The goal of replacing the

exemplars that are used as heuristics by both clinicians and researchers with causal models is therefore dangerously reductionistic because it suggests that those signs and symptoms that we cannot model do not exemplify the experience of the patient. This approach, in turn, threatens to exclude from psychiatry effective psychotherapeutic interventions that cannot be explained through cognitive neuroscience. The patchy nature of our best psychiatric models may be a necessary compromise between psychiatric research — a scientific endeavor — and clinical practice, an irreducibly humanistic and hermeneutic one.

Murphy faces another challenge: the defense of his two-stage picture of mental disorder in light of the role played by exemplars in psychiatric research. While I do not believe exemplars are the proper targets for psychiatric research, I do agree with Murphy that they play an important heuristic function in guiding, if distally, the *choice* of research targets. Accordingly, the source of exemplars becomes relevant to discussions about the objectivity of psychiatry. Murphy's hope is that psychiatry can establish new, solid exemplars through an objective process of fact-finding followed by a sober assessment of the nature of the normal and the pathological is unrealistic. In fact, I argue, the RDoC demonstrates the impossibility of creating a space for psychiatric research without referring to disease norms. The signs and symptoms patients present with provide an operationalization of human suffering that is essential to the construction of psychiatric research targets. Much like the RDoC relies on theory-laden conceptual structures already in place in neuroscience, it also relies on the value-laden exemplars of clinical psychopathology. I maintain that this use of exemplars is unproblematic as long as their status as heuristics, rather than reified kinds, continues to be recognized.

The myth that psychopharmacological knowledge is sufficient to cure mental illness has led to a deep distrust of biomedical approaches among many non-medical clinicians and patients. In fact, psychiatry is a long way from the sort of high-level explanations of exemplars that could offer up “cures” for mental illnesses. While psychiatric research will surely benefit from better integration with neuroscience, clinical practice as of yet bears almost no resemblance to “applied neuroscience.” By emphasizing a bottom-up approach in which clinical exemplars serve as distal motivations for research rather than direct targets, the RDoC has the potential to reintroduce psychiatric research as an ally and resource for clinical psychiatry. While we can be optimistic about the value of mechanistic explanations at the level of constructs, we cannot expect cognitive neuroscience to provide new exemplars any time soon. Clinical practice must continue even in the absence of complete biomedical explanations of its objects, and in certain cases (e.g. reactive depression, personality disorder, and other conditions that resemble non-medical problems in living) neuroscience and genetics may never have much to say that is useful. The RDoC can facilitate the selection of appropriate research targets by recognizing the humbling magnitude of the challenges of applying science to the mind.

Schizophrenia or the detours of the history of psychiatry: perspectives from the German psychiatry in the last third of the nineteenth century

Yazan Abu Ghazal, Institute of the History, Philosophy and Ethics of Medicine

“Schizophrenia is among the last of many aliases for a somewhat heterogeneous group of mental disorders the pathology of which is still unknown, the etiology unsettled and the outcome uncertain.” (Ellery, 1941) This assertion made by the Australian psychiatrist Reginald Spencer Ellery in 1941 aptly summarizes the fractured nature of our current knowledge about the reality of the syndromes subsumed under the designation “dementia praecox” (Kraepelin, 1896) or “the group of schizophrenias” (Bleuler, 1909). The years separating us from the publication of the schizophrenia volume in 1932 (Bumke, *Handbuch der Geisteskrankheiten*), in which the Heidelberg circle of psychiatrists developed that widely accepted and unified picture of schizophrenia as an organic cerebral disease, have not brought us any closer to discovering the physical underpinnings of this disorder. The disease process, which researchers expect to illuminate the dark recesses of the disordered

mind, but which the most painstaking research has so far failed to demonstrate, seems to be so subtle that all attempts to grasp it are doomed to fail. Furthermore, the discontent with the frustratingly slow progress characterizing the actual state of their field has led a growing number of scientists to think that psychiatric research needs an entirely new conceptual framework for understanding mental disorders. However, no one knows exactly what this new framework will look like.

By emphasizing the unpredictable character of scientific progress in psychiatry, my talk attempts to picture the place that the unknown occupies in psychiatric conceptualization. More specifically, it explores the ways in which the unknown shapes psychiatric research and reveals itself as a constitutive part of psychiatric classifications. In this regard, essential parallels exist between the current situation and the state of German speaking psychiatry in the last third of the nineteenth century. In this context, my talk delineates the detours followed by psychiatric research, and illustrates how, paradoxically, the progress in nosology hindered considerably the future development in psychiatric theories.

As a matter of fact, the reorganization of psychiatric knowledge at the turn of the twentieth century ensued from Kraepelin's clinical classification of psychoses. Within just few years, this reorganization succeeded in giving psychiatry a new form that is still used until the present day. Ironically, Kraepelin's simple clinical scheme based on the dichotomy between "dementia praecox" (schizophrenia) and "manic-depressive insanity" (cyclothymia) succeeded to replace the significantly more differentiated nosography that dominated psychiatric research in the last three decades of the nineteenth century. Kraepelin's classification of psychoses brought thus a radical simplification. Psychiatric diagnosis, which revolved around the framework of the "unitary psychosis", became particularly protean primarily in the years following the death of Wilhelm Griesinger in 1868. Moreover, it is remarkable to note that the real course, which led to Kraepelin's dichotomy, was not anticipated at that time, although all the components of the upcoming development were already available shortly after Griesinger's death.

In my view, the unpredictability of the development of psychiatric theories necessitates a reflection on the problem of the methods and foundations of psychiatric classifications. By analyzing this particular but constant and fundamental problem for the philosophical understanding of pathology, the first part of my talk examines attempts made by German speaking psychiatrists in the last three decades of the nineteenth century in order to apprehend the rationality and regularity of psychopathological phenomena. In this connection, psychiatric classifications are considered both as answers to questions that psychiatrists had to formulate in a language they had to shape, as well as tools to approach the unknown and the difficulties resulting from the unclassifiable in mental pathology.

The second part of my talk examines the theoretical framework underlying the nosographic intention in psychiatry. It argues that approaching the unclassifiable in psychiatric research relies above all on the complementarity of different methods and different points of view. Based on the psychiatric work of Griesinger (*Pathologie und Therapie der psychischen Krankheiten*, 1861), this part analyzes how the convergence of the neurophysiological, psychological and clinical sciences within the theoretical framework of the "unitary psychosis" first enabled the conception of "mental illnesses as diseases of the brain". Of special value in this connection is the significance of Griesinger's endeavor to develop a psychopathological oriented psychiatry that counteracted his early neurophysiological program from/of the 1840s.

I conclude my talk with some reflections on the role of perspectivity in psychiatric research and on the reasons why the forms of thought in nineteenth century psychiatry have proved to be very lasting.

Meaning and meaninglessness in psychiatric disorder

Norman Poole, Centre for Humanities, King's College London

A core problematic for psychiatry is the meaningfulness or otherwise of the phenomena with which it deals. Some, especially psychodynamically orientated psychiatrists and cognitive behaviour therapists, hold that psychiatric symptoms are really meaningful behaviours or states, which require empathy and understanding. In contrast, a biologically orientated psychiatry adopts the model that has served neurology so well: psychiatric symptoms are the outward manifestation of neurological dysfunction. Like the Jacksonian march that can occur during an epileptic seizure, actions have no meaning beyond their usefulness to the medical practitioner as a sign of pathology. The phenomena are thus said to be meaningless. The former accuse the latter of practicing a 'mindless' psychiatry while they in turn are accused of being 'brainless'.

The dichotomy was most cogently articulated by Jaspers in his *General Psychopathology*. However, he valued the insights gleaned from both perspectives. For Jaspers, the problems that patient presents with must be understood in the context of his or her own life, culture and developmental history. This understanding (*verstehen*) can be static and genetic. The former refers to a description of the form of a mental state, which is approached phenomenologically, while the latter relates to the emergence of one mental state from another. The conception of meaning Jaspers worked with was heavily borrowed from the hermeneutic methods of Dilthey. Sometimes though a phenomenon seems to defy our understanding (*un-understandability*), in which case he attributed it to an underlying biological dysfunction.

This view resonates with Wittgenstein's in *On Certainty*, a series of brief interconnecting thoughts about the nature of our foundational beliefs – logically indubitable, non-falsifiable, un-speakable, revealed only in our actions – which he terms 'hinge propositions'. So called because these foundational beliefs are the hinges on which all enquiry turns, they are the scaffolding (or 'grammar') that makes all meaning possible. If someone were to question or even just express a hinge proposition this is for Wittgenstein grounds to question his sanity: 'If Moore were to pronounce the opposite of these propositions which he declares certain, we should not just not share his opinion: we should regard him as demented' (OC 155). Intriguingly for psychiatry, the certainties that Moore was referring to – 'I have a body', 'here is my hand', 'I am sitting in my office' – are indeed frequently doubted by psychiatric patients, especially those with an 'organic' syndrome. There seems to be a parallel between Jaspers and Wittgenstein such that the break down of meaning signifies profound psychiatric disturbance, perhaps of a biological nature.

Daniel Dennett appears to come to a similar conclusion. He has famously argued that complex systems allow explanation from physical, design and intentional perspectives. The intentional stance assumes the system is rational; it believes and desires those things it ought to believe and desire. Although much can be said about this we are assured a full normative account of human rationality is now underway, which Dennett calls Intentional System Theory. When an individual fails to conform to this rationality, explicitly citing mental illness as a case in point, he advises the intentional stance be abandoned in preference for the design stance.

Donald Davidson is another philosopher within the analytical tradition who has developed an influential and comprehensive theory of meaning, which is grounded in Tarki's truth theorem. The aspects of his theory of meaning that are most relevant to psychiatry are the Principles of Charity and Humanity. The former demands that in an act of trying to understand another we take as the correct interpretation the one that maximises truth and coherence, thereby presupposing rationality in the other. The latter principle obliges us to assume that the other person holds beliefs that are by-and-large similar to our own. Some pathological beliefs, such as nihilistic delusions where the sufferer insists he is in fact dead, appear, at least on the face of it, to challenge these principles. And if they do then the person should, by Davidson's account, be considered irrational and no longer expressing meaningful propositions. Clearly this has significant implications for the manner in which psychopathological symptoms and signs are understood and potentially the treatment of psychiatric disorders.

Despite the importance of language and meaning for many strands of philosophy over the past century and the often controversial role played by the ascription of meaninglessness within psychiatry, it is perhaps surprising that the two literatures have only recently been brought to bear on one another. Dr Poole's doctoral thesis aims to explore these three philosophers' accounts of meaning and their relevance to psychiatry. In this seminar he will set out each of the theories and contrast them with Jaspers' own. He will highlight similarities, differences, theoretical commitments and consequences for each of these major Twentieth Century philosophers' theories of meaning.

Session 5 – How does medicine combine different types of evidence and different types of explanations ?

Science, Argument and Clinical Trials

Jonathan Fuller, University of Toronto

Today more than ever, epidemiology is the queen of the medical sciences. In terms of scientific articles, it is mostly population studies that populate the clinical journals read by clinicians. In the clinic, 'evidence' most often refers to the results of epidemiological studies. In fact, evidence-based medicine (EBM) tells us that we should look to epidemiological evidence rather than pathophysiological theory to ground our medical decisions whenever possible [1].

The production of evidence is a matter for medical science, while the application of evidence is a matter for (evidence-based) medical practice. Yet evidence-production is often driven by the demands of practice and thoughtful evidence-application requires an understanding of the science. Medical evidence, as a shared commodity, unites science and practice. Meanwhile, the philosophy of medicine stands to make important contributions to the philosophy of science, to epidemiology and to medicine by exploring the many dimensions of medical evidence, including the epistemic and logical.

For most of our modern therapies, therapeutic decision-making relies on epidemiological evidence of treatment efficacy. Therapeutic reasoning can be seen as a chain of inferences or serial argumentation, beginning with study data and ending in bedside predictions. The chain usually starts with data from randomised, controlled trials (RCTs) because they are widely accepted as the preferred studies for demonstrating causation, and treatment predictions are ultimately causal predictions. In an RCT, study participants are randomly allocated to two or more groups. Randomisation makes it likely that all groups start off with an equal prognosis. The intervention under investigation is then given to one group, while placebo or alternative therapy is given to the other groups. Statistical comparison among groups determines whether the intervention under investigation had an effect with respect to our chosen outcome.

The randomised, controlled experiment can be represented by an argument from positive results and special assumptions to the causal conclusion that the treatment is 'clinically effective': the difference in outcome among trial groups is a treatment effect. Clinically effective interventions cause the outcome in some proportion of a population - representing the effect size - that is always less than 1. Nancy Cartwright has shown this argument scheme to be deductively valid [2]. Given the right premises, the causal conclusion is fully entailed. As the argument justifies the claim that the RCT has superior 'internal validity', I call it the internal RCT argument. I make the case that internal validity is best understood as deductive validity.

While the internal argument makes an interesting claim about causation in the trial context, it makes no claim about the various clinical contexts that physicians encounter. We still have to get here from there, which is the job of our external RCT arguments. External arguments must overcome the problem of 'external validity' [3] confronting RCTs that recruit participants using strict eligibility criteria. The trial population is typically not representative of populations in which we wish to use our interventions. Nor is the trial environment representative of typical clinical environments. The basic question is thus, do these RCT results apply to this particular target population?

External RCT arguments are usually a transportation or generalization of the average treatment effect measured in the trial to the target population of interest. I reconstruct a few candidate external arguments from the medical literature. Some external arguments are statistical generalizations from a sample population to the wider target population; this is commonly the case in clinical practice

guidelines, which make wide generalizations. The assumption of representativeness is needed to license statistical generalizations. Other arguments are hypothetical and invite attempted refutation of the generalization; this is the approach advocated by EBM. It is presumed that certain measures of the average treatment effect are generally generalizable to other contexts. If compelling reasons to defeat the presumption in any particular case are not found, then the generalization is acceptable.

Scientific considerations, including trial eligibility criteria, experimental design, and underlying theoretical assumptions, figure prominently in both internal and external RCT arguments. Scientific reasoning is important not only for epidemiology but also for EBM. Epidemiology and EBM certainly share conceptual foundations and argument schemes. As a result, when we are reasoning around epidemiological evidence, the line between science and practice becomes relatively indistinct. I question whether we should in fact consider EBM a science. I conclude by exploring the implications of this discussion for the perennial debate concerning medicine's status as art and/or science.

References

1. Straus, S. E., Glasziou, P., Richardson, W. S. & Haynes, R. B. (2011) Evidence-Based Medicine: How to Practice and Teach it. 4th ed. New York: Churchill-Livingstone.
2. Cartwright, N. (2007) Are RCTs the gold standard? *BioSocieties*, 2(1), 11-20.
3. Rothwell, P. M. (2005) External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet*, 365(9453), 82-93

Radical transformation of China traditional medicine in Japan – Epistemology in East-Asian traditional medicine

Hajime Fujimori, Institut d'histoire et de philosophie des sciences et des techniques

TBA

The Myth of Placebo Additivity: Taming the Efficacy Paradox in Randomized Controlled Trials

Marco Annoni, University of Milan, Department of Health Sciences, European School of Molecular Medicine, European Institute of Oncology

The randomized double-blind placebo controlled trial (RCT) is a fundamental pillar of the contemporary biomedical edifice. Ever since its first introduction, the RCT has been considered the gold standard to test the efficacy of experimental medical interventions. For this reason, the approval of new drugs by national and international regulatory agencies is conditional upon the proof that such interventions have been demonstrated more efficacious than placebo in at least one high quality RCT. More recently, the growing attention generated by the popularity of evidence-based medicine (EBM) has provided the rationale to extend the logic of RCTs to other research fields such as sociology or economics. In this talk I will analyze the case of the "efficacy paradox", claiming that the logic upon which RCTs depend rests on the unwarranted assumption that placebo effects are stable across trial arms and across diverse trials. The paradox, I will argue, cannot be easily dissolved, for it descends from the very idea of relying on RCTs as a test for efficacy.

RCTs are a particular kind of scientific experiment in which a group of participants is randomly assigned to receive either the intervention to be tested (active group) or a placebo (control group). In this context, the word "placebo" stands for something that resembles the tested intervention in every respect but one, i.e. the specific effect that is hypothesized to bring about patient relevant outcomes. The logic of placebo controls, thus, is that of excluding any non-specific effect in order to isolate the

neat efficacy of the tested intervention. “Non-specific effects” is a general terms comprising diverse variables, such as the natural course of diseases, the statistical phenomenon of “regression to the mean”, and the biases introduced by placebo effects elicited by participants and researchers' expectations. After a trial is completed, the results in the two groups are compared. If the active group shows a statistically significant improvement over the control group, then the tested intervention is said to be more efficacious than the placebo. Accordingly, in order to assess the specific efficacy of the tested intervention, one needs to subtract the improvement measured in the control group from the one measured in the active group. The underlying logic of RCTs is simple, but has far-reaching implications for biomedicine and society. Yet it rests on an unquestioned assumption: that non-specific effects are stable across the active and the control groups, and across diverse trials for the same conditions. In fact, if the placebo effects in the active and control arms of the trial are not equal, then no comparison is possible. Consequently, one cannot isolate the true efficacy of the tested intervention.

The logic of RCTs, thus, rests on the assumption that placebo effects are additive to treatment's specific ones. However, this may not be the case. As a growing body of studies suggests, placebo-induced non-specific effects in trial arms (and across trials) may differ in significant ways. This is because placebo effects are context-dependent and may be large, sometimes more than treatments' specific effects. This may lead to what has been labeled the “efficacy paradox” of RCTs, of which there are two versions. The first version of the paradox obtains when a given treatment is compared to a placebo, and non-specific effects are high in the placebo group, but negligible in the active group. In this case, placebo effects may create a “ceiling effect” of treatment's efficacy. The paradoxical result is that an effective treatment may result ineffective despite its being tested according to the highest EBM standards. The second version of the paradox arises when two treatments are compared. Suppose we have two treatments for the same condition, X and Y, each tested in a different RCT. Treatment X is marginally more efficacious than placebo X, while treatment Y is largely more efficacious than placebo Y. Hence, we will say that treatment X is not efficacious, while treatment Y is. However, suppose that the magnitude of the non-specific effects across trials varies by a great deal, so that in trial X they are very large while in trial Y they are negligible. In this case we may achieve the paradoxical situation that placebo X is more efficacious than treatment Y. Thus, in both versions of the paradox an effective treatment is found to be less efficacious than placebos like dummy pills or sham acupuncture. This conclusion has severe consequences for both clinical research methodology and clinical practice.

The thesis that I will defend is that the efficacy paradox is real, significant and calls for a global reassessment of the way in which a certain class of medical interventions is tested in RCTs. It may hinder not only trials in complementary and alternative medicine, but also other trials testing for conditions in which placebo responses are known to be high—such as pain, mild depression or nausea. Furthermore, it cannot be easily resolved, for this would mean giving away with RCTs altogether. What needs to be done, instead, is to deploy a series of appropriate epistemic technique to mitigate its possible confounding effects. Drawing upon recently published works in the field of philosophy of medicine and empirical science, I will put forward the view that we may control for the efficacy paradox by implementing a three-step strategy. First, we need to acknowledge that the paradox is real but has limited applicability: not every condition or trial can be confounded by placebo effects produced by people's expectations. Second, we may change the trial design—using for example a “balanced placebo design”—to detect and disentangle expectation bias, thus preserving the trial internal validity. Third, we may need to integrate evidence coming from more than one source. RCTs are a powerful epistemic tool, but they are not the only one at our disposal. As I will show, other methodologies such as cohort studies, high-quality observational studies and N-of-1 trials may sometimes represent equally informative and reliable strategies to produce clinically useful evidence about treatments' efficacy and side-effects.

The status of mechanistic evidence in Evidence-Based Medicine

Jennifer Bulcock, Rice University

In 1992 evidence-based medicine (EBM) became the dominant paradigm for the practice of medicine. One of the primary factors influencing this shift was the growing distrust of "pathophysiological rationale" or, in other words, the use of mechanistic reasoning for making treatment decisions. As a consequence, EBM has systematically devalued and discouraged the use of mechanistic evidence in clinical decision-making and has prioritized the use of difference-making evidence generated by tightly controlled comparative clinical studies. These values are reflected in EBM's evidence hierarchy with randomized control trials as the gold standard at the top and mechanistic reasoning either absent or at the bottom.

This paper argues that the current status of mechanistic evidence in EBM is due to an impoverished understanding of mechanisms in medicine. A qualified weak interpretation of the Russo-Williamson Thesis (RWT) (Russo & Williamson, 2011; Illari, 2011) will be defended along with the various roles it allows for mechanisms in EBM, including providing traditional explanations of disease mechanisms, aiding in hypothesis generation, providing evidence of patient relevant causal relations between interventions and outcomes (efficacy), and aiding in the generalization of results from comparative clinical studies (externalizability). Objections stemming from Jeremy Howick's (2012) two requirements for mechanistic reasoning to "count as sufficiently high quality to provide strong evidence" will be considered and addressed. Given the interpretation of the RWT argued for in this paper, recommendations will be made regarding how EBM's evidence hierarchy should be revised to reflect the role and status of mechanistic evidence in EBM.

In much of the EBM literature objections to mechanistic reasoning are rehearsed without careful explanation as to why a previously intuitive rationale and explanatory framework can no longer be relied upon (cf. Andersen 2012). Among the reasons why mechanistic reasoning is no longer sufficient for establishing causal claims are the unreliability of mechanisms under intervention, the inherent complexity of systems in the human body and the inability of mechanisms to accurately map them, and healthy and unhealthy mechanisms can function differently. Despite these issues, traditional mechanisms from biology are capable of serving a limited explanatory function in medicine. However, this function does not transfer and is not sufficient when one is concerned with establishing reliable patient relevant outcomes from an intervention. The remainder of the paper seeks to establish the proper role of mechanisms once the above limitations have been taken into serious consideration.

The Russo-Williamson Thesis holds that "causal claims need to be made on the basis of evidence of both difference-making (statistical associations, randomized controlled trials, etc) and mechanisms" (Russo & Williamson 2011, 568). Taken on its strong interpretation, the RWT requires one to have the usual difference-making evidence and mechanistic evidence to be able to establish a causal claim. This thesis can easily be disproven by historical examples of causal claims only requiring one or the other type of evidence (treating a large nodular goiter in the airway with radiation therapy only requires mechanistic evidence – Howick, 2012, 144). On the weak interpretation the RWT requires some mechanistic evidence for C causes E. Unlike the strong version, mechanistic evidence on this interpretation can include mechanistic evidence of other relevant mechanisms. This interpretation of the thesis is much easier to accept because it allows one to reference evidence from other related and established mechanisms. The only qualification made to the weaker thesis would be to forego the requirement of some evidence of each type in those cases where there is strong high-quality evidence of one type and any attempt to gain the other type of evidence would be unethical. Particularly, in cases where an intervention has historically had good results and there is high-quality evidence of an underlying mechanism, an attempt to acquire difference-making evidence appears misguided and unethical.

Howick (2011, 2012) is vocal in his objections to the RWT, but never explicitly considers the weaker interpretation. He does, however, argue for the acceptance of mechanistic evidence in EBM, but only if two desiderata are fulfilled: 1) “the knowledge of mechanisms upon which the mechanistic reasoning is based is not incomplete” and 2) “the probabilistic and complex nature of the mechanisms are explicitly taken into account when inferring from mechanisms to any claims that a particular intervention has a patient-relevant benefit” (Howick 2012, 144). The second desideratum is unproblematic and ensures the appropriate use of mechanisms in EBM. The first desideratum is objectionable on the qualified weak interpretation (QWI) because it requires complete knowledge of the particular underlying mechanism whereas the QWI allows for evidence from any relevant mechanism. Additionally, on Howick's account, mechanistic evidence would only be considered for providing evidence of the efficacy of an intervention, which is in tension with this paper's assertion that mechanistic evidence has at least four evidentiary roles in EBM.

The roles of mechanistic evidence in EBM are split between traditional biological mechanisms and mechanistic reasoning in medicine. Traditional mechanisms can be used in EBM to provide disease explanations as well as aiding in the process of hypothesis generation. Those roles belonging to mechanistic reasoning in medicine are establishing efficacy claims as well as guiding the generalization of EBM guidelines generated by difference-making methods (externalizability). Mechanisms may contribute to the generalizability of such guidelines by using knowledge of the relevant mechanisms and how they may be affected by age, ethnicity, etc. to guide their choices in prescribing a given intervention for a particular patient.

Given the many ways mechanistic evidence contributes to clinical decision-making in EBM, revisions need to be made to the evidence hierarchy such that it is clear that mechanistic evidence can be as valuable as difference-making evidence both on its own and in conjunction difference-making evidence. One way to achieve this goal is to do away with the hierarchy and to make more nuanced recommendations for the decision-making process.

Andersen. 2012. “Mechanisms: what are they evidence for in evidence-based medicine?”

Howich. 2012. *The Philosophy of Evidence-Based Medicine*

Illari. 2011. “Mechanistic evidence: Disambiguating the RWT”

Russo & Williamson. 2011. “Epistemic Causality & Evidence-Based Medicine”

Abstracting and Abstractions in the Medical Sciences

Lara Keuck, Institut für Philosophie der Humboldt-Universität zu Berlin, Institut für Geschichte, Theorie und Ethik der Medizin, Universitätsmedizin der Johannes Gutenberg-Universität Mainz

In this talk I discuss how practices of abstraction in medicine challenge the idea of unity in the medical sciences. The idea of unity not only relies on a common aim of research, for instance to better explain and predict the course of a disease, but also on a unified definition of the disease. In practice, however, there are many different ways how diseases are defined. The talk focuses on the tension between disease phenomena as common targets of research and the plurality of disease explananda in terms of the characteristics used for disease classification: what is the relation between the disease that we are interested in and the scientific concepts that we are dealing with in experimental settings?

I take the philosophical distinction between the complete and the abstract and between the concrete and the abstract as a starting point to argue that practices of building disease classifications as well as practices of identifying disease markers, or criteria for class membership, are practices of abstraction. In the talk, I introduce an account of abstraction in the medical sciences and discuss some implications of my analysis for the idea of unity, arguing in favour of a strong pluralism.

I address both the generation of abstractions and their application. By the first I refer to the practice of establishing general categories by comparing and grouping particulars, for example individual patients. The second, namely the application of abstractions such as disease classifications, denotes the identification of individually manifested diseases as diseases of a specific kind. By drawing on disease classifications, I examine principle requirements for the selection of classifiable characteristics, these being the need to be exclusive enough to allow for delineating between disease phenomena and phenomena that do not belong in the medical domain as well as delineating between disease phenomena that differ from each other in some relevant aspect. Furthermore, the selection has to be inclusive enough so that the characteristics that define the classes allow for building groups at all. Practices of abstraction are not only found at the level of building classes but also at the level of identifying characters that are necessary to build classes. I call both, the identification of characters as well as the establishment of disease categories practices of abstraction, because they exhibit essential features of philosophical accounts of abstraction.

Against this background, I identify essential epistemic strategies for the design of medical classification systems: to identify relevant properties of disease phenomena and to disregard their other individuating properties. Also, the selected properties need to be framed in terms that adequately describe the phenomena with regard to the aim of classification. From this analysis of disease classifications, I develop my account of abstractions in the medical sciences:

Abstractions in the medical sciences exhibit additional characteristics to being neither concrete nor complete, they also relate to notions of biological similarity and medical relevance. To date, there is no unified account of these notions. I briefly review the most common arguments for this pluralism: (a) diversity in epistemic interests, (b) theoretical and practical plurality, and (c) biological complexity and/or normativity or a combination of (a,b,c). My account of abstraction does not provide a (unified) prescriptive definition of biological similarity and medical relevance, but submits that any abstraction in the medical sciences refers to these notions in one way or another. Against this background, I argue that any analysis of the establishment and transformation of disease definitions needs to pay particular attention to how medically relevant and biologically similar characteristics are construed and how they are intertwined with certain scientific practices. It seems to me that this can be best done with an integrated approach to history and philosophy of medicine and the life sciences.

The main argument of the talk is that the relation between the phenomenon of interest and the local explanandum can be described as abstraction—and that these abstractions vouch for a strong pluralism. I acknowledge the epistemic function of framing the disease phenomenon in a way that allows it to be a good explanandum for a specific research approach. At the same time, my analysis poses the question of how exactly the plurality of explananda that refer to the same phenomenon influence the relationship between the different explanations. I conclude that a closer look at practices of abstraction and at the concept of abstraction in the medical sciences is necessary to understand how the very objects of medical research are formed and transformed and to evaluate what this implies not only for the (dis)unity of the medical sciences, but also for the integration of research results from different medical sciences.

Mechanistic and Topological Explanations in Medicine: the case of Network Medicine

Marie Darrason, Institut d'Histoire et de Philosophie des Sciences et des Techniques

Medical explanations have often been thought on the model of biological ones. Since, for the last twenty years, biological explanations have been increasingly viewed as mechanistic ones (Bechtel and Richardson, 1993; Machamer, Darden and Craver 2001), so have been disease explanations – that are frequently defined as mechanistic explanations of a biological dysfunction (Thagard, 1999, 2006; Nervi, 2010). In this talk, while certainly not denying the existence or the relevance of such

explanations in medicine, I will argue that topological explanations that have been described in ecology (Huneman 2010) or in cognitive sciences (Bullmore and Sporns, 2009) can also be found in medicine, as it is the case in network medicine.

Whereas mechanistic explanations consist in breaking down a system into entities and activities in order to consider the causal relationships that are responsible for the production of regular changes in this system from an initial set of conditions to a final one, topological explanations rely on the topological properties of a system (Huneman 2010). In order to provide a topological explanation for a given system, the system shall first be represented in an idealized space (usually, a graph or a network) where the parts of the system are represented as nodes. It is then possible to use graph-theoretical concepts such as hubs, modules, motifs or coefficient clusters to derive topological properties from the location of the parts in the space and from the way the nodes are linked together. Instead of depending on the physical and material features of its parts, the topological properties of a system depend on the location that these parts occupy in a given space. Instead of explaining the mechanistic interactions between the parts of the system, topological properties provide an explanation for the structure and the substructures of the system.

This is precisely the kind of explanations that network medicine (Barabasi, 2011), a recent discipline born from the synthesis between genomics, systems biology and network theory, provides. Network medicine makes use of various networks such as disease genes networks, protein-protein interactions networks, metabolic networks or viral networks. In this talk, I will focus especially on the diseasome (Loscalzo et al, 2007) and on its relationships to the interactome. The diseasome intends to represent the relationships between human diseases and disease-causing genes. By retrieving all the available information on disease-gene associations from the Online Mendelian Inheritance on Man (OMIM) database, it is possible to build two different graphs that are the two faces of the same coin. On the one hand, there is the human disease network, where diseases are nodes and two diseases are connected if they share a same gene in their physiopathology. On the other hand, there is the human disease gene network where genes are nodes and two genes are connected if they are involved in the physiopathology of the same disease.

These two networks demonstrate topological properties. For example, when looking at the degree of nodal connections (that is, the number of nodes to which a given node is connected), it appears that the degree distribution follows a power law, meaning that the diseasome is not a random network but a scale-free network. In scale-free networks (Barabasi, 1999), most of the nodes are loosely connected to each other, except for a few nodes with a very high degree of nodal connections that are called "hubs". Being a scale-free network is a pervasive topological property of biological networks (Barabasi 2004) that explains their robustness (Lesne 2010; Huneman, 2010). Roughly speaking, such a network is not easy to destabilize since any attack on most of the nodes will result in a local disruption of the network, bearing little (if none) consequences for the whole system. This topological property also explains the common genetic origin of many diseases and comorbidity: if being obese, an individual is more likely to get diabetes, since obesity and diabetes share common genes in their physiopathology.

But the analysis of the diseasome gets to another level, once the diseasome is compared to the interactome. The interactome, while still far from being complete, is supposed to represent every interaction that takes place in the human body: gene-gene interactions, gene-protein interactions, protein-protein interactions, etc. The comparison of the diseasome with the interactome shows that there are topological differences between human diseases genes and non-disease genes. For example, most of human diseases genes are not part of the main hubs of the interactome, they are at the periphery of the interactome, while most of the non-disease genes are in its center.

If the topological properties of the human disease gene network explain the robustness of the system and the common genetic origin of diseases, there are still major explanatory gaps in our understanding of the role that genes play in disease. For example, topological explanations allow us to understand why the human disease gene network is robust but it does not explain why the human disease gene network became robust and how human disease genes came to be at the periphery of the interactome.

So topological explanations are not complete explanations – they are an incentive for searching mechanistic ones.

In this talk, I will first show that network medicine mainly provides two topological explanations: an explanation for the robustness of human organisms to disease and an explanation for the common role of genes in disease. Secondly, I will argue that these topological explanations need to be completed by mechanistic explanations and I will give some insights on the mechanistic explanations that have been suggested to this end. Finally, I will insist on how topological explanations in medicine challenge the way we traditionally explain diseases: instead of looking for specific mechanisms for each individual disease, topological explanations push us to explain disease in general and to find common mechanisms to diseases.

Dynamical Models: a type of Mathematical Explanation in Neuroscience and Medicine

Lauren Ross, University of Pittsburgh

Kaplan and Craver (2011) have recently argued that in order for models to be explanatory in neuroscience they must “map” onto the molecular details or mechanism which produces the phenomenon of interest. They have argued these claims from a “mechanist” perspective and specified them with a “model-to-mechanism-mapping constraint” (3M) that all models in neuroscience must meet in order to qualify as explanatory. I argue that this position ignores “canonical models” in neuroscience that are similar to Batterman's (2002) conception of “minimal models” and which derive their explanatory power by abstracting from the molecular details. These models capture and explain the shared dynamical behavior of systems with different “mechanisms” and molecular make-up, such that if further molecular details were added into these models they would lose this explanatory capacity. These models provide more than mere predictions or descriptions, because they explain why neural systems with differing molecular details share certain behaviors and why knowing particular molecular details are irrelevant to such explanations.

I demonstrate the explanatory power of minimal models in neuroscience with a case study of class I neural excitability. The quadratic integrate-and-fire (QIF) model (also known as the theta model, Ermentrout-Koppel model, and canonical type I model) is considered a canonical model for all neural systems with type I neural excitability. In 1948 A. Hodgkin studied and identified classes of neuronal excitability, including type I and type II excitability. Type I neurons are capable of firing in response to low-levels of stimulus and increasing their firing with increasing amounts of stimulus. Type II neurons, on the other hand, only begin firing with larger amounts of stimulus and tend not to significantly increase their firing rate with increasing amount of stimulus. While many different types of neurons share type I neural excitability, they do not share a single molecular mechanism responsible for such behavior. Naturally neuroscientists have wondered how neurons of different molecular make-up all display the same type of excitable behavior. The QIF model allows for an explanation of this behavior.

The QIF model is a minimal model for type I neurons and while it describes their characteristic excitable behavior it is more than merely descriptive. The explanatory nature of this model is similar to Batterman's description of the explanatory nature of minimal models in physics. First, consider the universality class of all neurons that exhibit type I excitability. In this class there are different lower-level models that account for the excitable behavior of different neuronal systems (in regard to molecular details). These lower-level models map onto certain molecular features of these distinct neurological systems and provide an explanation for their excitability. These lower-level models share an interesting relationship with the “higher-level” minimal or canonical model. The lower-level models can be transformed into the canonical model by a mathematical piecewise-continuous transformation that preserves important features of the lower-level model. This transformation

represents an abstraction from the molecular details of the original model and, furthermore, all lower-level models that exhibit type I behavior can be transformed into the minimal model in this way. At this point we may want an explanation for the following question: why do all of these molecularly distinct neural systems exhibit type I excitability? These molecularly distinct systems all exhibit type I excitability because models of these lower-level systems can be mathematically transformed into a single minimal model that exhibits the same behavior. It is the relationship between these lower-level models and the canonical model that explains the universal excitability of these systems.

This work illuminates the explanatory role of non-mechanistic minimal models in neuroscience and indicates that such minimal models may also be useful in explanations of neuropathology. This would be to demonstrate a form of non-mechanistic explanation in neuropathology. Since minimal models, such as the one illustrated in this paper, will be useful in describing universal features of molecularly distinct systems, they will often be the model of choice in accounting for certain signaling patterns and synchronistic features of neural systems and may well account for various related neuronal pathologies, including epileptic events, tremors, and sleep disorders.

Understanding the role of minimal models and non-mechanistic explanation in neuroscience and neurophysiology can contribute to a better understanding the explanatory role of these models in neurological pathology and other biomedical sciences. The explanatory import of minimal models conflicts with the mechanists claims that the best or the most common explanations in neuroscience (and molecular biology) are explanations of mechanisms. Minimal models for type I neural excitability are explanatory in that they allow for explanations of universal behavior among molecularly distinct neural systems and they are an explanatory model that mechanist theories fail to account for.

Thematic Workshops IASPM 2013

Workshop 1 (Elodie Giroux / Marion Le Bidan): Health and disease concepts: is there still any relevance of their philosophical analysis?

Is there a future for philosophical analysis of health and disease concepts? If there is, what sort of analysis and to what purpose? In what extent this analysis has structured the field of philosophy of medicine, and will continue to? Conceptual analysis has long been prevalent in Anglo-American philosophy of medicine, alongside the debate on the value-ladenness of health concepts. The relevance of this method for these concepts and more generally the utility of such an analysis has been questioned since several years. But only more recently alternative approaches seem to appear which take other points of departure: they rather seek for an articulation of the analysis of health concepts with issues of disease ontology, disease classification and disease causation. The issue of the relation of the normal and the pathological has also rather become that of the specificity and autonomy of the science of pathology and of the central role of physiology in medicine. Will the importance taken by molecular medicine modify the historical and central role given to functional analysis? We also observe a renewal of the importance given to an articulation of historical, sociological and

epistemological approaches to these concepts. Furthermore it has also become necessary to specify the objective of the philosophical analysis of health concepts: is it to serve as a foundation for clinical practice through the determination of what is to be treated and what is not? Is it to modify and specify these concepts or more modestly to clarify their meanings and logical relations? Is it appropriate to seek a definition common to both science and medical practice with regards to a greater coherence, or, on the contrary, to maintain and reinforce the distinction between different concepts? These questions are intertwined with the more general one concerning the role of philosophy in medicine and of the analysis of health concepts in structuring the field.

Workshop 2 (Alain Leplège / Hidetaka Yakura): Knowledge and practice in medicine

The relationship between scientific knowledge and action is central to the modern conception of science since Bacon. In medicine, the problems surrounding this relationship are still salient. How should the laboratory relate to the "field" in clinical medicine and public health? How to assess the relevance of medical researches? How is it possible to take advantage of (to translate) the knowledge of invariant relationship between variables, especially when they take the form of probability functions, identified at the population level to treat individual patients? Is there a difference and if yes which one, between explicative and pragmatic research methodologies? How to generalize the results of studies in special population? These are some of the questions which might be addressed during this workshop.

Workshop 3 (Michel Morange / Smail Bouaziz): Plurality of explanatory schemes in medicine

The occurrence of competing explanations, and the way this competition is solved, has been extensively studied by philosophers of science. Far less studied have been the cases when the different explanations are not competing but rather coexisting, the reason being that there are of a different type. The coexistence of evolutionary and functional explanations in biology has been outlined by Ernst Mayr, but it is only an example of a far more general phenomenon. Such a coexistence is particularly obvious in medicine, and many of the contributions address this plurality of explanations, in the past or in the present.

The occurrence of this plurality of explanatory types raises different philosophical issues. How many different types do exist? Is the origin of this plurality epistemic or ontological? What is the relation between the occurrence of different explanatory types, and the existence of different disciplines? How long can this coexistence persist, and how does it disappear?