The background of the cover is a deep blue. In the upper left, the Brandenburg Gate is depicted in a lighter blue, semi-transparent style. To the right, a large, semi-transparent globe shows the continents of Africa and Europe. A series of thin, white, curved lines sweep across the image from the bottom left towards the top right, creating a sense of motion and connectivity.

October 13th - 14th, 2009
Charité Berlin Symposium

Evolution and Diseases of Modern Environments

World Health Summit | October 14th - 18th, 2009 | www.worldhealthsummit.org

Final Report and Symposium Summary

Final Report

Evolution and Diseases of Modern Environments

A conference workshop at the Berlin Charité October 13-14, 2009

In conjunction with [The World Health Summit](#)

Sponsored by the Volkswagen Foundation

with additional support from

The Humboldt University Institute for Theoretical Biology

The Berlin Brandenburg Academy of Sciences and Humanities

The Berlin School of Mind and Brain and

The Berlin Museum of Natural History

Organizer: Randolph M. Nesse

Director, Evolution and Human Adaptation Program, University of Michigan

Academic Coordinator: Ana Gomez-Carrillo de Castro

Department of Psychiatry, Berlin Charité

Charité liaison: Mazda Adli

Department of Psychiatry, Berlin Charité

Meeting Planner: Boris Schulte-Römer

KIT group

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- [Early Development and Reproductive Health Workshop Report](#)
- [Evolution and Mental Disorders Workshop Report](#)
- [Sanitizing the Hygiene Hypothesis Workshop Report](#)
- [Developmental Aspects Of Diseases Of Modern Environments Workshop Report](#)

Background

Declining rates of mortality from infectious disease in the past two centuries have dramatically changed the nature of disease in a change Omran called the “epidemiological transition.” In his famous 1971 article, he quoted Kurt Mayer, who said that “any meaningful interpretation” of these changes, must “draw on the theoretical framework of several other disciplines for assistance.” The role of evolutionary biology in understanding this transition has long been recognized, but never considered systematically. Thanks to support from Volkswagen Stiftung, this conference brings together world leaders to work together on how Darwin’s theory, 150 years old this year, can advance our understanding of diseases of modern environments.

Some diseases of modern environments are revealed simply because more people are living to older ages. Others, however, are becoming more common even when age is adjusted. In particular, the metabolic syndrome of obesity, diabetes, hypertension and atherosclerosis has become an epidemic that is sweeping the globe. Changes in diet and exercise are important, and will be a core focus of these workshops, however the full story turns out to be complex, with environmental influences on genetic mechanisms that must be understood in evolutionary as well as mechanistic terms. Environmental factors also interact with genotypes to influence the age of puberty, with subsequent substantial effects on child bearing, and rates of reproductive cancers. Mental disorders are often attributed to the stresses of modern environments, but the data to assess these hypotheses has not been easy to access or analyze. Perhaps most dramatic, enormous increases in inflammatory and autoimmune disorders such as asthma and multiple sclerosis may be related to deficits in exposures to worms and other organisms that have been our constant companions until recent years.

Research and public health approaches to diseases of the modern environment are just now taking advantage of an evolutionary analysis of how the mismatch between our bodies and modern environments can lead to disease. This meeting will assess what we know now, what we need to know, and new research strategies that take full advantage of our evolutionary knowledge. The idea for this meeting was suggested at a symposium on evolutionary medicine in early 2008 at the Berlin Institute for Advanced Study, co-sponsored by the Institute, the Otto and Martha Fischbeck Stiftung and the Humboldt University Institute for Theoretical Biology. The scientists present discussed strategies that would allow the field to flourish, and recommended organizing a series of workshops in which participants from around the world would have an opportunity to discuss specific questions about evolutionary medicine in detail. They suggested organizing several such workshops together to facilitate connections among those working on otherwise diverse topics. Representatives from the Volkswagen Stiftung expressed interest in supporting this venture, and the Charité 300th Anniversary Celebration and the World Health Summit provided the ideal associated meeting, venue, and logistical support.

There are already substantial funding and communication resources for work on evolutionary aspects of genetics and infectious disease, but researchers who study diseases of modern environments have never previously had a major opportunity to gather to assess the state of their field, and the next steps that are required. The Volkswagen Foundation provided funding to bring 80 scientists to Berlin for this meeting. World leaders in subfields related to diseases of modern environments were recruited to lead workshops on five specific topics. They invited 16

senior and junior participants from diverse locations to each of the five workshops. KIT meeting planners provided logistical support.

These workshops used a modified Dahlem format that minimized formal presentations in order to allow the participants to delve into specific questions. Participants submitted papers to share with other workshop members prior to the meeting, and the workshops framed preliminary questions in advance. A rapporteur took notes and wrote up the conclusions of the group, which have been published at ***The Evolution and Medicine Review***. Groups made additional plans for collaborative research and/or publications. The substantial time allowed time for members of each group to meet and talk with those from other groups advanced a core goal of the meeting—providing a venue for researchers in evolutionary medicine to get to know each other’s work and establish new relationships and collaborations.

Evaluations by meeting participants were consistently and strongly positive, with many reporting this was one of the most engaging and important meetings they had attended. The meeting was reported in a variety of media outlets, including an extended article in *Science*. It was by far the largest meeting to date of sophisticated scientists studying Evolution and Diseases of Modern Environments. It leaves a legacy of new connections and collaborations among researchers from diverse fields and countries.

The Meeting Program is on pages 4-16.

The reports from the five specific workshops are on pages 17-36.

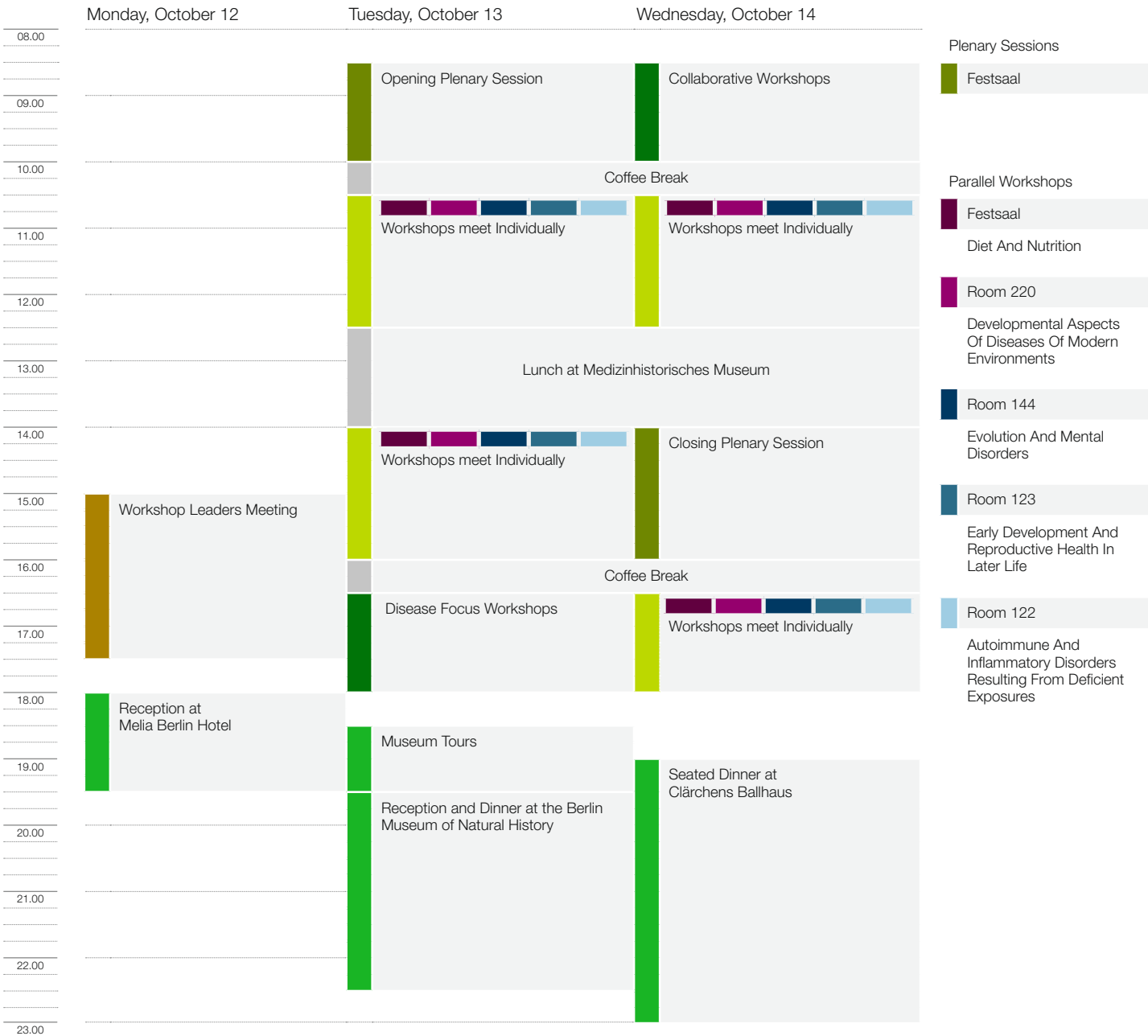


October 13th - 14th, 2009
Charité Berlin

Symposium

Evolution and Diseases of Modern Environments

World Health Summit | October 14th - 18th, 2009 | www.worldhealthsummit.org



Graduate School

08.30 – 18.00

Satellite Symposium

Evolution And Diseases Of Modern Environments

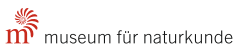
Hosts: Volkswagen Stiftung | Berlin Brandenburg Academy of Sciences and Humanities

Supporters: Berlin School of Mind and Brain | Berlin Museum of Natural History | Volkswagen Stiftung

Chair: Randolph Nesse | Director, Evolution and Human Adaptation Program | The University of Michigan

Academic Coordinator: Ana Gómez-Carrillo de Castro | Charité Universitätsmedizin Berlin | Germany

Meeting Planner: Boris Schulte-Römer | K.I.T. GmbH Association & Conference Management Group & Co. KG | Germany



In collaboration with
The Evolution & Medicine Review

Declining rates of mortality from infectious disease in the past two centuries have dramatically changed the nature of disease in a transition Omran called the “epidemiological transition.” In his famous 1971 article, he quoted Kurt Mayer, who said that “any meaningful interpretation” of these changes, must “draw on the theoretical framework of several other disciplines for assistance.” The role of evolutionary biology in understanding this transition has long been recognized, but never considered systematically. Thanks to support from Volkswagen Stiftung, this conference brings together world leaders to work together on how Darwin’s theory, 150 years old this year, can advance our understanding of diseases of modern environments.

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Research and public health approaches to diseases of the modern environment are just now taking advantage of evolutionary analyses of how the mismatch between our bodies and modern environments can lead to disease. This meeting will assess what we know now, what we need to know, and new research strategies that take full advantage of our evolutionary knowledge.

This conference has been organized following the model of the Dahlem conferences, in which formal presentations are de-emphasized, and extensive time is allotted for small groups of scientists to delve into the details of specific questions. Each workshop collaborates to write summaries of their areas of agreement and disagreement and what next steps will move the field forward. These will be published in *The Evolution & Medicine Review* (<http://evmedreview.com>). Based on recommendations from scientists at a recent evolutionary medicine meeting at the Berlin Institute for Advanced Study, five overlapping workshops will meet as a part of the conference to facilitate connections among those working on otherwise diverse topics. This format is itself an experiment, the results of which will be analyzed at the conclusion of our meeting, and presented at the WHS Thursday Symposium on Evolutionary Medicine.

Workshop

Diet And Nutrition

Festsaal

Leader: William Leonard | Professor of Anthropology | Northwestern University

It is widely assumed that many chronic diseases in modern societies arise because our bodies are poorly suited to eat the foods we prefer. Actually gathering and analyzing data on this question turns out to be very difficult. Several transitions in human diet are relevant: the rise of agriculture, industrialization, and recent trends to processed foods.

Questions to be addressed include:

- *Is there a distinctive dietary regime that characterizes the genus Homo or Homo sapiens? If so, what are the key characteristics of the human dietary strategy, relative to other primates and other mammals?*
- *What are examples of (and the evidence for) genetic adaptations to distinctive dietary/nutritional regimes in humans?*
- *How do developmental and epigenetic factors influence human nutritional health? How does the interplay between biology (genes, development, physiology) and culture/behavior shape (a) variation in human nutritional physiology and (b) the influence of diet on health outcomes?*
- *What are the key sources of information from "Comparative Human Evolutionary Biology" relevant for (a) understanding the links between nutrition and health, and (b) developing recommendations to promote human nutritional health?*

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Workshop

Developmental Aspects Of Diseases Of Modern Environments

Room 220

Leaders: Peter Gluckman | Head | Centre for Human Evolution Development and Disease Liggins Institute, University of Auckland

Mark Hanson | Professor of Cardiovascular Science | University of Southampton

Recent evidence reveals that vulnerability to atherosclerosis, hypertension, obesity and diabetes is influenced by early life events. The mechanisms for transmitting this risk seem to involve epigenetic mechanisms, and it has been proposed that the mechanism may have been shaped by selection. The importance of this topic to the current epidemic of chronic disease is obvious.

Questions to be addressed by this workshop include:

- *What evidence is there for epigenetic mechanisms and epigenetic inheritance systems playing a role in human disease across more than one generation?*
- *Is there any evidence for polyphenisms in human development ?*
- *How can concepts such as predictive adaptation be tested ? In animals? In humans?*
- *Do developmental arguments provide the basis for some of the inter-relating changing patterns of obesity, chronic disease and reproductive maturation? What studies seem indicated?*
- *How do developmental perspectives interrelate to the other topics of the meeting (life history/puberty, diet etc)?*

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Workshop

Evolution And Mental Disorders

Room 144

Leaders: Martin Brüne | Professor of Psychiatry | University of Bochum, Germany
 Alfonso Troisi | Professor of Psychopathology | University of Rome Tor Vergata

Evolutionary principles provide a missing foundation for understanding mental disorders. The contributions range from evolutionary perspectives on genetic contributions, to vulnerability, to evolutionary explanations of emotions and how selection has shaped the mechanisms that regulate them. This workshop will cover the role of modern environments, but it will also range more widely to assess several other contributions of evolution to psychiatry.

Questions to be addressed include:

- *Why is early environment so important in increasing vulnerability to mental disorders?*
- *What better explains the relevance of gene-environment interactions and correlations for the etiology of mental disorders? Vulnerability or plasticity?*
- *There are large age- and sex-related differences in the prevalence of psychiatric disorders. Are there evolutionary explanations for these epidemiological data?*
- *Is there a genuine increase in prevalence rates of mental disorders (in developed countries), and if so, why?*
- *As evolutionary psychiatrists, which directions does an evolutionary approach suggest for technological breakthroughs that could improve psychiatric therapy?*
- *Which methodological changes could an evolutionary perspective offer to the next generation of psychiatric research?*

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Workshop

Early Development And Reproductive Health In Later Life

Room 123

Leaders: Gillian Bentley | Professor of Anthropology | Durham University, UK
 Grazyna Jasienska | Professor of Human Biology | Jagiellonian University, Poland

Early life events also influence reproductive physiology and subsequent reproductive strategies. Research in this area is developing fast, with implications especially for reproductive cancers. Some early life conditions, such as obesity, precocious puberty and the development of polycystic ovarian syndrome also interact with risks for metabolic disorders. The connection with other workshops is clear.

Questions to be addressed in this workshop include:

- Which stages during development are important for when environmental effects might influence later reproduction and health.
- Why are these stages/periods of time important and how do they relate to overall physiological development?
- What mechanisms mediate between adult reproductive function and environmental/ecological factors?

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Workshop

Autoimmune And Inflammatory Disorders Resulting From Deficient Exposures

Room 122

Leaders: Kathleen Barnes | Department of Medicine | Johns Hopkins University
 Erika von Mutius | Professor of Pediatrics | University Children's Hospital, Munich

Certain diseases that have become more common in recent generations are mediated by immune abnormalities that are more common in people who lack early exposure to certain organisms, especially helminths. This is a topic of intensive study, with special relevance to asthma, allergic disease, and multiple sclerosis. This workshop will assess the state of evidence for such effects and recommend new research strategies.

Questions to be addressed include:

- *How strong is the evidence that lack of exposure to microbes and helminths increases disease risk? Which diseases? How do genetic variations influence risk?*
- *How far along are controlled trials of helminths for autoimmune disorders?*
- *What aspects of the immune system mediate these effects? Are there ways to influence them without administering helminth substances?*
- *Does exposure to other pathogens influence risk? What recommendations for parents of young children are justified by existing evidence?*
- *What epidemiological and genetic studies are needed to further specify the risks of living in an environment devoid of the organisms we have evolved with?*

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Reception at the Melia Hotel Berlin

Monday, October 12, 2009 | 18.00 – 19.30

The reception takes place in the Melia Hotel Berlin giving delegates the opportunity to strengthen old friendships and forge new ones in the relaxed atmosphere of a social environment. Take this opportunity to arrange informal meetings with friends and colleagues.

Friedrichstraße, 103 | 10117 Berlin



Dinner at the Berlin Museum of Natural History

Tuesday, October 13, 2009 | Museum Tours, 18.30 – 19.30 | Reception and Dinner, 19.30 – 22.30

This is a perfect opportunity to visit Germany's largest museum of its kind. With an area of over 6,000 sqm, Berlin's Museum of Natural History presents many rare and valuable objects illustrating the evolution of life. Enjoy the experience of having dinner next to the world's largest mounted dinosaur skeleton, a Brachiosaurus brancai.

Invalidenstraße 43, 10115 Berlin | In walking distance to the hotel (ca. 1,3 km)



Dinner at Clärchens Ballhaus

Wednesday, October 14, 2009 | 19.00 – 23.00

Have the benefit of a seated dinner in a quaint location in the heart of Berlin. The Clärchens Ballhaus is an insider tip giving the visitor to Germany's capital the possibility to catch a glimpse of the charm of a formerly famous ballroom from the turn of the century. During the week this hall is busy with multiple concerts, balls, dance lessons, and performances. Enjoy the allure of a location nestled in a neighbourhood famous for nightlife which has managed to rekindle the tea dance concept for a younger generation.

Auguststraße 24, 10117 Berlin | In walking distance to the hotel (ca. 1 km)

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Meeting Venue

Berlin School of Mind and Brain
Luisenstraße 56
10099 Berlin



Hotel

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Friedrichstraße 103
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Hosts



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AKADEMIE DER WISSENSCHAFTEN

Diet and Nutrition Workshop

Workshop Rapporteurs: Jay T Stock (U Cambridge) Claudia R Valeggia (U Pennsylvania)

Workshop Leader: William R Leonard (Northwestern)

One of five workshops in a conference on
[“Evolution and Diseases of Modern Environments”](#)
Organized by Randolph Nesse, at the Berlin Charité October 13-14, 2009
In conjunction with [The World Health Summit](#)
Sponsored by the Volkswagen Foundation

The following provides a brief summary of the discussions of the Diet and Nutrition Workshop at the Symposium "Evolution and Diseases of Modern Environments". Discussions were broadly based around two themes: (1) diet and nutrition in earlier human evolution, and (2) recent human evolution, dietary adaptation and the origins of "diseases of the modern world". A summary of these is provided below, followed by a discussion of the relevance of dietary trends in human evolution to understanding the etiology of diseases of the modern world, some general points of agreement between the participants, and proposed areas of future research.

Theme I: Diet in Earlier Human Evolution

The group was in broad agreement that during much of human evolutionary history there has been selection for increased dietary flexibility. There is evidence for occasional dietary specialization in hominin evolution (e.g., the Neandertals, being top-level carnivores based on isotope data); however, much of our dietary evolution suggests a broad range of food items.

The importance of so-called "fallback foods" was also widely discussed. Peter Ungar and Matt Sponheimer noted that these are secondary, low ranking food resources that are often relied on during periods of seasonal stress. There was wide agreement that it is these lower-ranking (often poorer quality) resources that most strongly shape nutritional 'adaptations' (i.e., dietary minima) over evolutionary time, rather than the "average dietary conditions".

In early hominin evolution, there is evidence for exploitation of tough foods, producing rapid tooth wear and selection for large molar tooth size, thick enamel and craniofacial robusticity. Recent chemical and microwear analyses suggest that the australopithecines were exploiting more cereals / grasses / sedges than previously thought. The emergence of early *Homo*, is associated with a reduction in mandibular size, robusticity, tooth enamel thickness, and buttressing of mastication. These changes suggest a shift in food use patterns and/or food processing. Early *Homo* specimens in different parts of the old world are variable in body size, raising questions about when human body size and proportions fully emerged. Many interpretations of the greater importance of animal foods with *Homo* are due to the ubiquity of stone tools and animal bones; however, more fine-grained analyses (e.g. bone chemistry) are required to provide clear evidence of a dietary shift to include more animal foods. Such resolution may be possible in the next 5 years, according to the paleontologists in the group. In addition to meeting nutritional needs, meat/animal foods also may have been associated with

assisting in the colonization of new environments for hominins, by allowing them to converge on a common dietary niche under different environmental conditions.

By the later stages of hominin evolution, we have compelling evidence of high levels of meat consumption in Neandertals, based on carbon/nitrogen isotopic analyses of bone collagen. In contrast to the Neandertals, Upper Paleolithic humans appeared to forage on a broader range of plant and animal resources, that varied widely based on local ecology.

With the origins of agriculture, there was a shift again to more extensive plant exploitation, including grasses - cereals / starch. There was some disagreement within the group about the extent to which humans have adapted/adjusted to the exploitation of cereal grains.

Overall, the shift from a 'paleolithic' to modern diet was clearly characterized by a reduction in protein content of the diet and a marked increase in carbohydrates, particularly simple carbohydrates (sugars). Many have also noted that within the last 50 years, there has been a particularly rapid increase in the amount of processed sugar added to the modern American diet. Whether this increase is largely responsible for explaining the dramatic increase in obesity rates in the US since the 1960s remains a point of debate.

Theme II: Recent Human Evolution & Dietary Adaptation

Genetic adaptation to human dietary regimes. A number of examples (and evidence for) genetic adaptations to distinctive human dietary practices were discussed. These included:

Lactase persistence: There was clear consensus that the ability to digest lactose past the weaning age is certainly a product of natural selection. However, there were differences of opinion and broad discussion on the nature of selection for lactase persistence. Mark Thomas argued that selection is episodic, acting mostly during the bad times and not so much during the good times. He proposed that consumption of milk and dairy products act as "buffering" for the bad times during farming lows. When the going got tough, lactase persistence allowed farming people to drink milk without getting diarrhea.

Lactase persistence appears to have originated in central Europe (Balkans) but, because of demographic changes associated with farming/dairy mixed techniques, its distribution gets shifted up North (e.g., Scandinavia). This is consistent with the archaeological evidence of the origin and spread of Linear Band Keramik [LBK] pottery in the European Neolithic. An additional point noted by Mark Thomas is that the spread the lactase persistence allele appears to be driven by demographic factors - that is population growth/expansion - rather than by differential changes in food use over geographic space.

In addition to the cultural hypothesis for the selection of lactase persistence, Loren Cordain presented a novel hypothesis on the possible role of lactase having an indirect effect on resistance to malaria. The malaria plasmodium needs to utilize the host's PABA (para-aminobutyric acid) to survive. Milk is very PABA-deficient, therefore a diet rich in dairy products may favor resistance to malaria. Lactase is preserved as a way to promote consumption of milk (which would protect the person) into adulthood.

Copies of amylase gene. The number of copies of the amylase gene has been offered as another example of human genetic adaptation to distinct foods (either wild or domesticated foods with high starch content, in this case). There was some disagreement as to whether this represents a valid example. The reported association between the number of copies of the amylase gene and starch content in the diet is not significant. There is a trend, but statistically the results are not robust. The question here is why is variation in number of the amylase gene copies maintained? Starch consumption could possibly be one reason, but starch is mostly digested in the intestine, not in the mouth (and this example is for salivary amylase).

Alleles for the Alanine-glyoxylate aminotransferase (AGT): This enzyme targets 2 different intracellular organelles. In carnivorous species, AGT targets mainly mitochondria; in herbivores, it targets the peroxisomes. Humans, being omnivorous, show polymorphisms that seem to correlate with the relative proportion of plant or meat in the diet. Some evidence to suggest that populations with greater recent ancestry of meat eating (eg. the Saami) have higher frequencies of the allele favoring the "retargeting" of enzymatic activity to the mitochondria.

Detoxification genes (Cytochrome P450). These include genes that code for enzymes with role in a wide range of metabolic processes. They are highly variable and have been hypothesized to be associated with diet breadth in human diets.

Tolerance to alcohol. Variation in the ability to metabolize alcohol has been proposed as another interesting case for genetic adaptation; however, there was not much consensus about whether it represented a good example. Part of the problem here surrounds the fact that the "primitive [ancestral] condition" for humans appears to be the ability to metabolize alcohol, with various groups [eg. Asian populations] then losing that ability. Hence, unlike the "lactose/milk use" model, there is not a clear "gene-culture" story with the ability to metabolize ethanol. Specifically, it is hard to develop a compelling adaptive argument for *losing* the ability to metabolize alcohol in certain populations, but not others. Is drunkenness, for example, considered such a negative social behavior that low tolerance was favored (selected for)? There was not much enthusiasm about this hypothesis.

Uricase. In human and great apes it appears there has been selection for genetic reduction in the activity of uricase, the enzyme that metabolizes uric acid (a byproduct of meat digestion). Some evidence to suggest that reduction in uricase activity was selected for under conditions of seasonal variation in food availability that characterized environments for our hominin ancestors. It was pointed out that humans have high uric acid concentrations, but they also have a higher flux of metabolism.

Skin color/Vitamin D Metabolism. Robert Perlman posed the question of whether genetic differences in skin color (& implications for vitamin D metabolism) likely represented a 'dietary adaptation'. A discussion of the group ensued about this about the association between skin color and vitamin D. Lighter pigmentation and lactase persistence go together. Are they selected for together? There was some disagreement on whether higher latitudes get enough vitamin D.

Origin and nature of "Diseases of the Modern World".

Finally, we discussed the nature of "diseases of the modern world" and the role the dietary factors play in their origins. There was wide agreement that the process of lifestyle and dietary 'modernization' does not produce the same health effects in all human populations. Rather, there seems to be remarkable disparities across different ethnic groups. Some populations respond with increases in the incidence of diabetes and metabolic syndrome in general (e.g., the Pima of North America), where others (e.g., Siberian populations) show low incidence of diabetes with westernization of diets, but show high incidence of hypertension.

We felt that understanding the nature of this variation is an important task for researchers in human nutritional evolution. Key unanswered questions include: What are the determinants of these differences in responses to diet changes? Is this due to genetic differences, social differences, epigenetic effects or a combination of all of these?

The first example of possible determinants was variation due to ancestry among women regarding fat oxidation: Caucasian women have better oxidative responses than African American. Discussion then ensued about differences in fat deposition patterns. Having fat in the wrong place seems to be what is causing health problems, Andreas Pfeiffer commented that some obese women do not develop metabolic syndrome and they are the ones that do not have large abdominal fat deposits. Low abdominal fat is correlated with better health outcomes, however Jonathan Wells pointed out that a certain amount of abdominal fat is essential for immune function. Fat has macrophages and may be important to fight disease in high disease-load populations. This can be what drives differences in fat deposition patterns across different populations.

Mike Power pointed out that adipose tissue, in addition to act as energy storage, contains enzymes that transform steroid hormones, which in turn affects reproduction and that has crucial fitness implications. This recent recognition of fat as more than simply a storage organ (playing important roles in both endocrine and immune regulation) has led us to see fat as playing a more dynamic role in shaping physiology and the origin of nutrition-related diseases. An important question identified about the role of fat in influence human health was: (a) how do such factors as sex differences, reproductive strategies, disease loads and ethnicity (biological and social dimensions) shape the variation in fat storage and the activity of fat?

There was agreement on the general statement that energy balance seems to be the key, i.e. too many calories and too little physical activity puts the body in a state of positive energy balance that drives the body metabolism to store the surplus of energy as fat. In fact, the amount of calories consumed does not seem to have changed much in the last 40 or so years, but the physical activity levels are dramatically low.

However, a few people in the group stressed the importance of differences in the quality of diet as also having a central role in the epidemics of obesity. Jonathan Wells proposed that the obesity epidemics in the US started with the American Heart Association promoting a low fat diet to prevent risks of cardiovascular disease, pushing people to eat a high carbohydrate diet. In

addition, the processing of sugars, in particular sucrose, in food manufacturing also changed the glycemic indices and the energy availability of diet items for the public.

Discussion went back to energy balance and the difficulty of measuring physical activity levels in different populations, as noted by Josh Snodgrass.

On an applied perspective, what is the best exercise regime for losing weight? Bill Leonard discussed the utility of looking at energy expenditure & workloads in traditional societies as a window onto both the amount of activity/energy expenditure in earlier human societies and the pacing of daily activities (i.e., The "tortoise vs. hare" phenomenon). Traditionally societies often display a slow and steady pace (as in walking long distances frequently) in maintained sustained increased in metabolic rate. Work in nutrition suggests that this strategy works better in promoting energy balance and weight stability in the modern world. Andreas Pfeiffer noted, in contrast, that high intensity exercise is good to develop muscle mass and increase BMR, but sustained exercise burns fat.

There was agreement in that human populations experienced a major shift in macronutrient composition during modern times (what is modern?). We are now eating much more processed carbohydrates than before. This has the potential to skew things towards high prevalence of obesity.

General points of agreement across the discussions were:

There is no 'ideal' Palaeolithic diet for humans. Dietary recommendations should include a knowledge of the evolution of the human diet and recent adaptations, but rather than there being an 'optimal' human diet, there are a range of adequate diets which depend upon individual biological and cultural variation.

There is considerable variation between populations, which are based upon genetics, developmental and epigenetic factors, and cultural context. It is the combination of these factors that interact with modern diets to lead to different health outcomes with the dietary transition. Proposed human diets should be targeted to both biological and cultural factors, collectively considered as ethnicity.

We should not consider caloric content of diets in isolation of total lifestyle, both factors are important in combating modern metabolic diseases.

Epigenetics and early development are likely to be key factors in the origin of modern metabolic diseases. Further research is needed on the relationship between developmental factors and adult health outcomes. Additionally, interventions are best targeted in early life.

Questions that remain unanswered include:

What explains the variation in obesity levels across and within populations? Particularly, what are the relative roles of (a) genetics, (b) epigenetic and developmental factors, and (c)

social/political/economic factors. Clarification of these issues should be the focus of future research.

Explaining population variation in changes in nutritional health with modernization

Does industrialization largely have the same impact regardless of the setting? Or do we see particular clustering in different populations in transition? There is mounting evidence coming from different settings that although overweight and obesity tend to increase dramatically with a change in diet and lifestyle, the impact that this has on health varies both within and between populations. That is, not everybody is experiencing and responding to nutritional and lifestyle transitions in the same way.

The observed ethnic variation in how the nutritional transition impact health arises from genetic differences, environmental differences, and the combination of both. Strict genetic control seems to be unlikely in the majority of obesity cases. In fact, genetic differences can explain only about 5% of the variation in morbid obesity. Genes may explain the disease, but cannot explain the development of the disease in a particular person. Furthermore, it is clear that the metabolic response to increased energy availability is a polygenic phenomenon: there are lots of genes with small effects involved. For example, at least 20 genes have been identified as being related to diabetes, but each of them explains very little of the variation in the development of diabetes. Epigenetic effects are the most likely culprits.

Environmental factors are contributing relatively more to the equation. Given the pivotal role of nutrition during early development, a life course approach to the study of this variation generally yields a clearer picture of the possible determinants of population and individual differences.

There are certain "life course experience" variables that have been shown to be associated with adult health, particularly with risk for obesity: among others, birth weight (as a proxy of prenatal nutrition), pattern of infant and childhood growth, amount of exercise, and infectious disease burden.

Our group went on to discuss how our understanding of population variation in responses to the nutritional transition can be applied to concrete medical advice^[1]. Ethnicity was mentioned as an important determinant, but what do we mean by ethnicity?. It was agreed that ethnicity, by all accounts, should be interpreted as individual/personal history, which includes your genetic background, your culture, and your life experience. A given nutritional status is, therefore, the embodiment of all these variables. Cultural practices, particularly those related to food preferences and taboos, were mentioned as crucial elements in the design of recommended healthy diets for individuals, as they are intimately related to compliance issues. Food is indeed identity and cultural values must be incorporated. In sum, there is no single paleodiet that will be the magic bullet. Rather, individual diets need to be tailored to recent past history and individual life course experiences.

A life course approach is paramount. Nutrition has the highest "programming" impact when human growth is most plastic: during prenatal growth and early postnatal growth. Thus the importance of maternal nutrition during pregnancy and of infant feeding practices. Growth

restriction *in utero* coupled with rapid catch up growth has been strongly associated with higher risk of cardiovascular disease. Breastfeeding has been shown to have programming effects as well. Breastfed infants develop better insulin management mechanisms than bottle-fed ones. The immunological effects of breastfeeding are as important as the nutritional ones for explaining the long term developmental consequences.

What aspects of the evolutionary perspective are particularly important to incorporate in mainstream western medicine and public health?

The concepts of trade-offs and of a life course approach are key for reorganizing the medical paradigm.

Ancestry, understood as a result of biocultural forces.

Nutriomics and nutrigenetics (Andreas Pfeiffer). However, most in the group said that developmental history is more important than knowing the genetics of an individual.

What research can be emphasized to reinforce those aspects?

Studies of migrant populations in which parents, children and grandchildren have different developmental histories, particularly with respect to nutritional availability and disease load.

Studies of populations in transition in different settings (circumpolar, tropical, subtropical) and with different original subsistence practices (hunter-gatherers, agriculturalist, pastoralists).

Studies that look closely at infant feeding practices and weaning food choices (both in present populations and in historical and pre-historical ones via bioarchaeological analysis).

[1] We called this "Richards' conundrum" in reference to a question posed by Michael Richards during our discussion. Michael will give a presentation about the evolution of diet to an audience that includes First Nations communities. He wondered whether the findings about ethnic differences in the response to dietary shifts can allow us to safely say to an First Nations individual that, because of his/her ethnicity, he/she had certain higher risks for nutritional problems.

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Session leaders: Gillian Bentley and Grazyna Jasienska

In session: Gillian Bentley, Benjamin Campbell, Kathryn Clancy, Marco Del Giudice, Vivette Glover, Grazyna Jasienska, Diana Kuh, Shanthi Muttukrishna, Pablo Nepomnaschy, Alejandra Nuñez de la Mora, Janet Rich-Edwards, Norah Spears, Hamish Spencer, Beverly Strassmann, John Wiebe

Rapporteurs: Kathryn Clancy and Benjamin Campbell

In evolutionary medicine so far, a lot of emphasis has been placed on understanding disease, and with the exception of cancer reproductive function is especially understudied. We want to look at the relationship between early development and adult reproduction but we have little data. Those of us in this session have an evolutionary, ecological perspective but few have also thought about a broader health perspective to combine both disciplines. Preliminary discussions identified nutritional status and psychosocial stress as crucial to this combined perspective, and could provide a direct link to evolutionary medicine.

We first sought to define "stress" and largely arrived at the idea that one way, for the purposes of this session, is to define "stress" as anything that activates the HPA/limbic system. We also tried to clarify the difference between stressors and stress, and the measurable outcomes relevant to fitness/reproductive success. We focused on the female reproductive system as an incredibly plastic system, perhaps more plastic than any other process in the body. We tried to turn towards some of the main "stages" in order to get a sense of what is already in the literature, what it tells us, how it may or may not be biased (in terms of where we focus our research attention) and where we should thus direct future research.

For the first session we focused more on age at menarche as a stage and perhaps biomarker that we could use as a way to get at 1) environmental predictors of variation, 2) variation in reproductive outcomes and 3) seemingly competing hypotheses. For instance, we have support to suggest that early psychosocial stress leads to early menarche, but also that early good nutrition leads to early menarche. However, individuals who have early menarche due to good nutrition will be larger, and thus it is less of a trade off than when early psychosocial stress drives an earlier move to reproduction. Further, this is context-specific, it's about whether you can afford this trade-off or not.

In the second session we discussed the Predictive Adaptive Response (PAR) and other hypotheses that may explain reaction norms in reproductive physiology. Our conversation was

inconclusive. In large part this was due to the fact that we were unsatisfied with the degree of evidence in the literature, particularly of a longitudinal nature, that will help us test competing hypotheses. We noted that the PAR's emphasis is on prenatal exposure but that doesn't mean PAR is exclusive to the prenatal period. We also noted problems in use of rodent models because they are short-lived and have different life histories – perhaps we find epigenetic/intergenerational effects in rodents but that doesn't mean we can find them in humans. Ultimately, long-lived species have a continuous plastic response: perhaps we can think about the fetus making the best decision it can: there is some reduction of variation after that decision, but still plasticity after fetal programming.

On the second day, we broke into small groups that focused on reproductive maturation, fertility and pregnancy as processes to put most of our attention.

In our reproductive maturation group, discussion centered on separating effects of adrenarche (onset of adrenal androgen production) and puberty. While the hormonal processes associated with these two events are clearly separate, their relationship to obesity may be coordinated. Recent work in child development has focused on the importance on the interval between adrenarche and pubarche as crucial for socialization including sexual behavior and gender roles. Thus there is an urgent need to study and understand the impact of modern environments and obesity on earlier maturation, and a possible shortening of the window between adrenarche and pubarche, on socialization, sexual behavior and gender roles. Cross-population studies are crucial to establish baseline patterns of the relationship between adrenarche and pubarche and their importance to socialization.

In the pregnancy group, two important issues we considered were pregnancy loss and pre-eclampsia (hypertension during pregnancy) because of the ecological perspective we can offer. In addition to chromosomal abnormalities, nutritional status or psychosocial stress could impact the degree of fetal loss, and while significant work has been done on the maternal-fetal conflict in pre-eclampsia, we also want to offer the perspective that modern environments and overnutrition could provide additional important insights. We also know very little about population variation in either of these conditions, and propose future research in this direction for hypothesis testing and assessment of baseline variation.

The fertility group's main conclusion was that we need to bring our particular approach to variability to medicine. We have discussed variability and its importance throughout this symposium but we need to better define what we mean and why we consider our approach so important to medicine. The main problem we note is that we are uncomfortable making strong recommendations to medicine regarding reproductive health because we do not yet have enough baseline data of the normal range of variation within and between women and within and between populations. The focus in funding mechanisms is on basic molecular science and disease-focused science, and our discipline falls between these two extremes. Thus we first propose a greater emphasis on research that assesses normal variation in the following ways: longitudinal, repetitive sampling, an assessment of lifestyle factors, documentation of ethnic and geographic variation, and a focus on the major lifestyle transitions as these can be periods of major variability. For instance, important transitions include cycling to pregnancy, or lactational amenorrhea to resumption of fecundity. Finally, we wanted to point out that the population that

the majority of our data is western and economically developed, and that they represent the most extreme and highest concentrations of ovarian hormones (and likely other indicators of reproductive function).

One recommendation we did want to make, or at least propose as a hypothesis, is that we should reduce pharmacologic interventions in young women. In many industrialized countries the majority of young women are on hormonal contraceptives for supposedly abnormal cycling, when they are usually experiencing adolescent subfecundity. However hormonal contraceptives increase young women's exposure to exogenous hormones and their possibly mitogenic activity in the breast and other tissues, thus possibly increasing their risk of breast cancer. This is contrasted by the possibility that this intervention is beneficial in premenopausal women with established cycling, at least in industrialized environments, because the exogenous hormones may be lower than the endogenous levels and thus, by disrupting the HPO axis, lower women's exposure. We want to be clear that we recognize the importance of hormonal contraceptives for actual contraceptive use, but we strongly suspect its off-label use for cycle regulation far outstrip its contraceptive use in certain populations. It is for this reason that our emphasis on the exploration of normal variation is of such urgent importance. We would like to see a move towards non-pharmacologic intervention, such as intervention in lifestyle, in those situations where young women are experiencing discomfort from which they would like to be relieved. However, we also suspect that many young women who seek help for "abnormal cycling" are suffering from misinformation about what constitutes normal, and correct information about the fact that their bodies are operating well may go far in reducing their concerns.

From the perspective of evolutionary medicine the study of reproductive function is relatively undeveloped. At its current stage the most crucial tasks are to increase our knowledge of normal variation in reproductive processes, to study populations cross-culturally, and to examine lifestyle transitions and early environments as containing stages that can have a significant impact on later reproductive outcomes.

Developmental Aspects of Diseases Of Modern Environments

Workshop Summary by

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To give focus to the discussion, the workshop primarily addressed the issue of the role of developmental plasticity in contributing to human health and disease, and in particular on the relationship between early life events and the later risks of cardiovascular and metabolic disease. In general a poor start to life, as reflected in maternal conditions, is associated with a greater risk of insulin resistance and hypertension in later life. Increasingly it is also recognised that maternal obesity has consequences for the offspring. It has been known for several decades that gestational diabetes is associated with effects in the next generation — a phenomenon that was originally referred to as developmental programming or metabolic teratogenesis. The word ‘programming’ continues to be used in the biomedical literature to refer to developmental effects with later consequences, but our workshop preferred to avoid such terminology and instead consider the extent to which developmental plasticity can influence chronic disease risk. A key starting point for our discussions was the various conceptual models based on evolutionary principles that have been proposed to explain these relationships. These are built on our current understandings of developmental plasticity and epigenetics.

Most of the discussion centred on conceptual models that posit that developmental plasticity in response to cues in early life has adaptive value, not necessarily just for immediate fetal advantage, but also for advantage that extends postnatally or is only sometimes exhibited postnatally. These have been variously referred to as anticipation, forecasting, prediction or learning models. Anticipation can be incorporated into the genome by genetic assimilation if the

exposure is invariable (e.g. the development of the thickened heel pad in infants), but where the exposure is not invariable, plasticity may be more appropriate and under active selection. A general model that has been proposed, with some variations in emphasis, is the learning/anticipatory/predictive model, which states that because there are costs and constraints that limit the capacity to maintain plasticity throughout life, the early offspring alters its trajectory of phenotypic development for potential advantage across its life course.

The nature of the cue and relationship to outcome was discussed at length. In comparative biology cues can be either rather non-specific or have very specific trait-related outcomes. In humans the former appears more likely, with the cues (probably mainly stress and nutrition) involving some degree of inertia integrating the maternal experience. The more severe the cue, the more immediate the response of the developing organism will be (e.g. intrauterine growth retardation, premature delivery). Clearly the outcome will be affected by the developmental period during which the environment is perturbed. The induced advantage may occur early in postnatal life but extend into adulthood. Examples of such posited advantage in response to an anticipated adverse environment cued *in utero* include increased neonatal insulin sensitivity (and thus adiposity in infancy, which has been proposed to buffer the growing brain against predicted nutritional adversity at or after weaning), an altered life history pattern (including early puberty, which may be interpreted as an appropriate response to a high extrinsic mortality risk), altered appetite control, reduced lean body mass and later insulin resistance to match the organism to an anticipated nutritionally impaired environment. Tradeoffs might include less investment in repair such that longevity is reduced. But as the individual ages, the fidelity of prediction must reduce and indeed its fitness value is reduced once reproduction has been achieved. Thus the appearance of metabolic disease in middle age may be influenced by such processes, particularly given the marked increase in nutritional density in modern environments.

The discussion addressed the extent to which anticipation is an important feature of developmental plasticity and considered alternate models. There are many comparative examples where adaptive advantage of plasticity has been demonstrated or inferred in plants, bacteria and all eukaryotic taxa. In particular a central question was: to what extent are the effects of fetal plasticity adaptive, versus being a failure to buffer? Does it matter that a plastic trait evolved through adaptation? A challenge is how to identify signatures of adaptation in plasticity. If epigenetic changes can be shown to be functional/clustered rather than stochastic, they are more

likely a result of adaptation. As yet we have no capacity to identify the signatures of natural selection on epigenetic markings.

Thus the presumption of the adaptive value of plasticity in humans must be based on comparative arguments. Plasticity and canalization are universal features of biota. Clearly it is important to understand how a system evolved irrespective of whether it is adaptive or not, taking account of how the life history and ecological context of the species will have shaped appropriate patterns of response.

A summary of the clinical/experimental evidence was iteratively combined with an evaluation of its theoretical significance. Developmental induction of later metabolic risk is seen in individuals within the normal range of birth sizes and without obvious impact on the fetus or mother, and is affected by physiological stimuli, such as nutritional status before or at conception and during pregnancy, or the nature of infant feeding. This excludes teratogenic effects, suggests a role for anticipatory processes and excludes arguments that have been put forward based on concepts of conflict — namely that the fetal response is primarily for maternal benefit — a concept that gained no traction in the discussion. Adaptive strategies are likely to differ in monotocous versus polytocous species, and maternal benefit may be more likely in the latter. Any disadvantage of such anticipatory induction generally requires a mismatched (high postnatal nutrient) environment and occurs at >35 years of age, and is therefore unlikely to be under negative selection as in evolutionary terms reproductive success has likely been achieved. Indeed, there is little evidence for any adverse fitness effects, bearing in mind that evolution acts to optimise fitness, not health or longevity.

In reviewing the data it was emphasised that complex phenotypes are induced/altered, that at birth in humans epigenetic changes can be seen, and that in late adulthood epigenetic echoes can be observed that in turn reflect the prenatal environment (e.g. the Dutch famine). Preliminary evidence was presented relating the early epigenetic state to later phenotypic trajectory. It was noted that the phenomenon is remarkably easy to replicate in every mammal studied. Several theoretical models have been presented based on a ‘thrifty adaptation’ *in utero* — however it was pointed out that these have been based on a false premise of fetal insulin resistance; in fact increased insulin sensitivity is a feature of being born small, and insulin resistance does not develop until after infancy. This is also true in several animal models.

An emergent different set of developmental experiences, namely that of the consequences of maternal diabetes and maternal obesity, was discussed. Both are associated with a higher risk of obesity in the offspring. While the effect of gestational diabetes is well recognised and understood in terms of effects of fetal insulin on adipogenesis, less is known about the mechanisms of maternal obesity leading to offspring obesity. Adaptive arguments do exist and it may be that there is no need for a different conceptual framework to explain this phenomenon; however much more research is needed.

Discussion was held as to the significance of epigenetic inheritance, which was distinguished from other forms of non-genomic inheritance. There are several ways in which trans-generational environmental influences could occur, not all involving epigenetic inheritance, and indeed the evidence for trans-meiotic transfer of epigenetic marks is limited except in the case of small RNAs.

This review of the clinical and experimental data informed consideration of the theoretical concepts. We noted that generation length (20–25 years) is *the* temporal unit of selection and that anticipation is common/universal across taxa. Given this, objections to anticipation models where there is benefit across the pre-reproductive and reproductive phases of the life course based solely on the issue of the time to some potential benefits being measured in years were generally considered ill-founded. Maternal effects are common and generally confer some fitness benefit on the offspring, although the evidence is of variable quality. Conflict theory and imprinting were discussed. It was generally considered that maternal-fetal conflict models were overstated and the evidence for a role of fetal-maternal genomic conflict in humans, unlike some of the better-documented examples in rodents, was weak; in contrast weaning conflicts were assumed to be common in humans.

There are costs and constraints that limit plasticity, and hence the potential role of anticipation is based in part on exposures particularly during critical windows. The fitness costs of mal-prediction are only costs if they occur before and during reproduction, and any fitness benefit of predictions can occur either before or during reproduction. Indeed we favoured a model in which trajectories of development were altered giving potential benefit across the life course. Plasticity theory shows that predictions need not have high fidelity to be selected for, and if the fitness costs of mismatch are asymmetrical then the fidelity of prediction can be very low and yet be under strong selection. For example, if the fitness disadvantage of being developmentally

mismatched in a high nutrition/low threat environment is much lower than the failure to predict a low nutrition/high threat environment, then anticipation of a low nutrition environment will be favoured.

Other considerations that merit interaction between empiricists and theoreticians included the role of both spatial as well as temporal environmental variation across the life course, the relative role of adaptive plasticity in generalist and specialist species, and the relative role of non-genomic and epigenetic inheritance in matrilineal and patrilineal populations/species.

Given the limitations on testing hypotheses regarding fitness and adaptation in humans, the potential value of modelling as well as the comparative approach was emphasised throughout the workshop.

Evolution and Mental Disorders

Report from a Workshop led by

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Alfonso Troisi, Professor of Psychopathology, University of Rome Tor Vergata

Workshop summary by rapporteur Daniel Stein, University of Capetown

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Participants in our group on mental disorders had a broad range of academic backgrounds, including psychiatry, psychology, medicine, evolutionary theory, genetics, epidemiology, economics, and philosophy.

The group aimed to follow a number of rules of engagement outlined at the start; we were not merely nice about one another's theories, nor were we simply oppositional, and we asked all to participants to contribute in roughly equal measure.

We attempted to address 6 questions:

- Why is early environment so important in mental illness?
- What better explains the relevance of gene-environment interactions/correlations for the etiology of mental illness: Vulnerability or plasticity?
- Has there been a genuine increase in prevalence rates of mental disorders, and if so, why?
- There are large age and sex-related differences in prevalence of psychiatric disorders. Are there evolutionary explanations?
- What directions can evolutionary medicine suggest for psychiatric treatment?
- What methodological changes can evolutionary medicine suggest for psychiatric research?

The first question, then, is why is early environment so important?

This question, however, raises additional questions eg “what is early?”, and “what is mental illness?”. Michael Ruse called this later question “the elephant in the room”. A key issue is that reproductive success (R/S) (a crucial outcome for evolutionary theory) is not the same as health.

We spent a good deal of time on the question of whether evolutionary theory could help define mental illness, and were unable to reach full consensus. On the one hand, many argued that by helping to define the science of emotions and their dysregulation, evolutionary medicine could contribute to such a decision. However, there was also a significant emphasis in the room that judgments of mental illness also entail social values that are a step removed from the concerns of evolutionary science.

In tackling the question of why early environment is so important, we noted that *homo sapiens* is characterized by a unique life history; we have a particularly long developmental period, and this then creates many possibilities for dysfunction. At the same time, our particular environment creates significant constraints, and we develop in an optimal way to cope optimally with these constraints. Indeed, we also noted, in a way that is somewhat skeptical of conventional approaches to understanding pathology, that we should not simply think of humans as susceptible, like machines, to environmental stressors which cause breakdown. In particular, there is tremendous resilience; humans are typically able to respond to whatever environments we are in, in adaptive ways.

This immediately leads to the question of gene-environment interactions. There have been significant advances in understanding the ways in which particular genes and particular environments interact to lead to subsequent psychopathology. At the same time, there is much to learn; multiple genes may have small effects, and not all data on G x E interactions have been replicated. We noted that alleles can be risky vs healthy in different environments (eg, in an adaptive way) and that alleles are expressed differently in novel environments (eg, in a non-adaptive way). Methodological problems include how to assess the extent of allele variation, and how to measure outcomes. We agreed that where there are common genes and common disorders, then we must look a great deal to environments to help explain susceptibility to mental disorders.

From a skeptical point of view, the question was raised of to what extent research on gene-environment explanations of mental disorders was really part of evolutionary medicine. One argument was put forward that all such work on genetic variation ultimately should be conceptualized as part of evolutionary medicine, insofar as it emphasized individual variation and its consequent trade-offs. However, a counter-argument was made by some that in order for

particular work to be a central component of evolutionary medicine one necessarily needed data on reproductive success, and this was typically not available in psychiatry.

We agreed that there was not a great deal of data on changes in prevalence of psychiatric disorders over time (eg we have little data on psychopathology in hunter-gatherer or other early populations). Perhaps there has been an increase in the prevalence of autism, and there is certainly evidence for changes in the pattern of substance use over time. Arguably anorexia is one disorder of modernity, having increased markedly in recent times in countries with western values and perceptions of beauty. Internet disorders may be another disease of modernity. The problem of determining whether there has been a change in prevalence of psychiatric disorders over time is compounded by the difficulty in defining boundaries of disorder. While epidemiological data does not necessarily lead to a conclusion that psychiatric disorders are disorders of modernity, the universality of phenomena such as anxiety and depression are consistent with a perspective that highlights their adaptive value.

We noted gender and age differences in the prevalence of psychiatric disorders. It seems clear that evolutionary explanations are important in understanding such differences (consider, for example, the different nature of sexual disorders in males – where so-called sexual addiction is more common, and in females – where anorgasmia is more common). However, there are a range of different evolutionary theories about gender and age differences in psychiatric disorders, and deciding between them will require further work. Also, we also acknowledged that more knowledge of proximal factors to explain gender and age differences, both biological and cultural, is needed.

There was again some disagreement on the question of what evolutionary medicine could offer in the way of psychiatric treatments. There was clear agreement that evolutionary medicine offers a theoretical basis for understanding the role of emotions, of motivational structure, and of human cooperation and conflict. There was also clear agreement that psychotherapy could be improved by a more integrative approach to understanding the doctor-patient relationship, behavioral ecology of symptoms (eg bereavement), functional analysis of behavior, goals/strategies of treatment. It was also argued that an evolutionary medicine approach is useful in normalizing symptoms, and in enhancing empathy for patients.

However, there was disagreement about the extent to which a therapy was simply “evolutionary”. For example, all good psychotherapies might draw on evolutionary principles

(eg emphasizing the importance of the doctor-patient relationship). In terms of medication, the argument was put forwards that evolutionary medicine could be particularly important in analyzing the trade-offs of treatment (eg pluses/minuses of SSRIs for depression). However, a counter-argument is that treatments must be judged simply on the basis of the extent to which they are efficacious. For DSM-V, it is not wholly clear how evolutionary medicine can contribute, although clearly DSM-V needs improvement.

In terms of future research informed by evolutionary medicine, several ideas were put forwards. For example, we need to better research adaptive phenomena, defective phenomena, and their interaction. We reviewed Nesse's work on depressive symptoms, Badcock's work on imprinting in autism/schizophrenia, Troisi and Brune's work on non-verbal behavior, and their implications for future research in these areas. We discussed recent work by Rook and colleagues, who have put forwards several ideas for future investigation of psychiatry-immune presentations.

Evolutionary medicine can help refine particular hypotheses in a range of different psychiatric areas. Importantly, it provides, we thought, an integrative and rigorous framework for approaching problems – emphasizing the adaptive value of human variation, the complexity of interactions between people and their environments, and the pros and cons (trade-offs) of negative emotions. Epidemiological studies need to include more sophisticated dimensional measures, and to perhaps to include intermediate functional behaviors.

***Sanitizing the hygiene hypothesis:
Health lessons from human co-evolution with microorganisms***

**Report from a Workshop led by
Kathleen Barnes, Department of Medicine, Johns Hopkins University and
Erika von Mutius, Professor of Pediatrics, University Children's Hospital, Munich**

One of five workshops in a conference on
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Introduction: There is a large body of research work addressing the potential beneficial role of microbial exposures for the development of asthma, allergies and autoimmune disorders. A seminal publication by David Strachan in 1989 coined the 'hygiene hypothesis' in an attempt to explain his observation of protection from hay fever when having many older siblings. The 'hygiene hypothesis' has since undergone numerous revisions and alterations with respect to potential underlying immunological mechanisms, the type of infectious / microbial stimuli and the potential link to autoimmune diseases. It has become apparent over the years that many open research questions have not been answered; therefore, we have drafted a qualitative overview on the existing evidence of a protective effect of microbial exposures for the onset of asthma, allergies and autoimmune diseases.

Evidence: The Working Group agreed there is compelling evidence from population-based studies in humans to suggest that the 'hygiene hypothesis' may be operative in asthma, allergies, SLE, sarcoidosis, and ankylosing spondylitis, and suggestive evidence exists for type I diabetes, inflammatory bowel disease (IBD) and multiple sclerosis. The most robust effects for asthma and allergies have been observed for helminths, hepatitis A and bacteria with their compounds, whereas there is still considerable debate with respect to tuberculosis in epidemiological studies. The Working Group also felt also identified suggestive evidence for exposure to malaria and the development of SLE. In addition to population-based studies, many experimental studies, mostly in murine models, have been undertaken to study the relationship between microbial exposure and allergic and autoimmune diseases. NOD, BALB/c, EAE and IBD mice as well as dogs have been used as models, the later for studies in eczema. A variety of exposures has been investigated, such as helminths and their compounds, bacteria and their compounds, ligands for innate immune receptors, and viruses.

Potential mechanisms: Potential mechanisms for this relationship are likely to involve immune responses, in particular the balance of pro- and anti-inflammatory mechanisms and the induction of innate and adaptive regulatory responses. The genetic background of an exposed person is likely to play an important role. Various genes have been implicated in these diseases, a number of which overlap across diseases. Variation in the HLA region has repeatedly been observed. Multiple non HLA loci are also likely to contribute with small effects. The evolution of the

human genome will most likely have occurred under strong microbial and infectious pressures varying according to biogeography. But environmental changes may also strongly have contributed to the incidence of allergies and autoimmune diseases. The most compelling evidence suggests an important role for childhood farm exposure, improved sanitation and decreasing family size. The eradication of helminths and the modification of flora and fauna may also have played a role.

Gaps in knowledge :

There are numerous unknown mechanisms and inconclusive findings to date. The scientific community lacks well-designed epidemiological studies relating increased or decreased microbial exposures to the incidence and prevalence of autoimmune diseases and mental disorders, all of which are associated with immune dysregulation.

We know little about the relevant exposures. The potential role of viruses has not been explored. Standardized approaches for the assessment of environmental microbial and allergen exposures are lacking and must urgently be developed. There is large uncertainty with respect to the potential beneficial effects of probiotics: Do they have an effect? How do probiotics interact with gut microbiota? Which strains should be selected for clinical trials? Also, very little is known about other dietary substances affecting the gut microbiota.

The timing of exposure has been shown to be critical in experimental and epidemiological studies. Yet, we still do not know whether prenatal or postnatal exposures matter and what the significant time windows of exposure are for conferring an effect.

The Working Group also felt that the use of comparative animal models has not sufficiently been explored among both wild and domesticated animals, including non-human primates, and can be investigated under varying environmental exposures,.

With respect to mechanistic studies, the simplistic Th1 / Th2 concept must be refined. The Group felt that T cell plasticity in the context of microbial exposures demands more attention and that potential interactions of immune responses with endocrine and neuroendocrine systems should be taken into account. Finally, gender differences and sexual selection have not been investigated. Reproducible gene-environment interactions on well-characterized and sufficiently powered populations also need further attention. The use of gnotobiotic mice may help to unravel mechanisms in immune regulation. There was consensus that a major limitation in the understanding of underlying mechanisms was the inaccessibility of target organs in humans.

Finally, there is an urgent need to investigate potential consequences of medical interventions such as treatment with antibiotics and paracetamol (acetaminophen), eradication of helminths, and the supplementation of vitamin D and folic acid.

Applications:

Prevention: Several studies using animal models of allergic and autoimmune disease have been successful in the prevention of these diseases by exposing the animals to infections and microbial

products. We can learn more about dose, potential side effects, and mechanistic pathways to eventually translate such substances into safe pharmacological preparations for use in humans. Based on these studies, novel prevention strategies can be developed in the future.

Therapy: Initial trials with helminths (*Trichuris suis*) has shown benefit in inflammatory bowel disease patients. However, the administration of live microorganisms may not be practicable for large scale treatment in the future. Studies in animal models have shown that substances isolated from microorganisms account for the therapeutic effect; therefore, the effective substances of microbial origin can likely must be identified in well-designed studies and translated into pharmaceutical preparations for use in humans.

Recommendations: We consider it too early to provide recommendations on an individual level with respect to personal hygiene. However, we strongly feel that this field of research is advancing rapidly and will offer innovative approaches to treatment and prevention of a number of inflammatory diseases in the near future. A consensus is that western countries have experienced drawbacks of life styles deficient in microbial exposures which are likely to result in allergies and autoimmune disorders. Therefore, potential consequences of public health measures to improve sanitation and hygiene should be recognized in developing countries.