2015 Journal of Physiology meeting with Dr Denis Noble

00:23
so welcome to this conversation
00:26
in fact Dennis Mike and myself thought
00:31
that no one's going to turn up and we're
00:34
going to go down to the bar and have the
00:35
conversation so instead I'm ready
00:38
pleased that we've got an audience my
00:42
name is David Patterson and I'm
00:43
editor-in-chief of the Journal of
00:45
physiology and about a year ago just to
00:48
set the framework as to why we're having
00:50
this session this evening is that we
00:54
published just over a year ago in the
00:58
journal a special issue which was
01:02
focused on the integration of
01:05
evolutionary biology with physiological
01:07
science and we were really quite
01:09
surprised in the reaction that we got
01:12
when we published this particular issue
01:15
so a lot of information came in to us
01:18
over the web over blogs and we really
01:22
felt for this audience at this meeting
01:25
we wanted to share some of the narrative
01:27
that took place because this is pretty
01:31
controversial as you'll see in a moment
01:34
and so the format this this is not a
01:37
blue corner in a red corner with a
01:39
debate that in ox and Oxford we call

01:44
this a conversation so what we're going
01:48
to do I'm going to fire a few questions
01:51
at my colleagues here and we're going to
01:56
have this conversation and then the plan
01:58
is maybe halfway through if we run out
02:01
of steam we're going to open it up to
02:03
the audience and you can fire some
02:05
conversation fire some information at us
02:08
so we all know that physiology has
02:13
really been the prince or princess of
02:17
the biomedical sciences that underpins
02:20
medicine and new discovery hence the
02:23
Nobel Prize is in Physiology or medicine
02:28
but in the last 25 years that's become
02:31
evident that the subject area as a
02:33
discipline
02:34
has started to turn into a bit of a
02:37
Cinderella subject often being viewed as
02:40
a phenotyping tool for the genomics and
02:45
genetics communities so we're going to
02:49
discuss now with two leading opinion
02:53
leaders in the field am i right
02:55
Dennis Noble emeritus professor of
02:58
physiology at the University of Oxford
02:59
and also current president of the IEEE
03:02
ups Dennis is a prolific writer in this
03:06
area his best-selling book the music of
03:10
life has really set the scene for the

03:13
debate with the reductionists on my left
03:17
in the blue corner is Mike Regina well
03:25
known to this audience professor of
03:28
anesthesiology at the Mayo and also a
03:30
prolific writer and opinion leader in
03:34
the field of integrated physiology so
03:42
what we're really concerned about is a
03:44
little bit of history why did the wheels
03:47
come off physiology 25 years ago
03:49
why has the mantra molecule to man
03:55
essentially failed to deliver some of
03:58
the big promises that were talked about
04:01
in terms of new medicines and cure for
04:04
disease and finally why has the
04:10
inconvenient truth of data often been
04:14
ignored and influential circles
04:16
especially in the higher echelons of
04:19
funding biomedical research where today
04:23
the world has taken a very Jean centrism
04:26
view of the evolution of disease so this
04:30
is the framework of the conversation and
04:33
I just like to kick off maybe with you
04:36
Dennis to start with and ask a pretty
04:40
simple question that is a probably got a
04:42
very complex answer but you know what
04:46
what is a gene
04:49
well let's be clear I'm gonna give a
04:52
simple answer actually David let's be

04:55
clear nobody knows however let me
05:00
clarify that statement just a little
05:02
because I don't think you'll be
05:03
satisfied with that it's defined today
05:07
of course in terms of DNA and nobody can
05:10
doubt the importance of the genome I
05:14
think though it's been misdescribed
05:17
it's best described as a database used
05:20
by organisms to enable them to generate
05:25
the functions that you and I and others
05:28
study as physiology and what we have to
05:32
remember in opposition to the gene
05:35
centric view is that in order for that
05:38
to be the case we inherit much more than
05:41
our DNA we inherit number one the whole
05:45
of cell structure which is self
05:47
templating it doesn't need DNA to self
05:49
template many of you probably don't know
05:52
cells can actually divide without a
05:54
nucleus we inherit many forms of RNAs
05:58
which determine part of the way in which
06:01
the genome is interpreted we inherit
06:03
many forms of epigenetic marking and I
06:06
don't need to tell this audience how big
06:09
the field of epigenetics has now become
06:12
we also inherit behavioural marking of
06:16
the genome there examples of all of
06:18
these those are what we necessarily

06:20
inherit in the short-term generation to
06:23
generation to generation in the longer
06:26
term even more fundamental changes are
06:29
inherited in changes in the genome
06:32
itself with various forms of genome
06:35
reorganization in response to challenges
06:38
from the environment so I think the
06:40
short answer David is we inherit much
06:43
more than DNA DNA is extremely important
06:46
sequencing was very important too but
06:48
it's not the be-all and end-all of
06:50
understanding function in physiological
06:52
systems amplify that a little bit the
06:57
word gene didn't come about till around
06:59
1909 or 1902
07:01
19:10 and it has become an effort to
07:05
reconcile heritability estimates from
07:08
the population genetics people who if
07:11
your mother is this tall and your father
07:12
is this tall how much of the variance
07:14
can we understand in the in the
07:15
offspring with molecular genetics and so
07:18
there's been about five or six distinct
07:21
definition of what makes a gene since
07:23
1909 at one point it was sort of a black
07:26
box unit of phenotypic inheritance that
07:30
explained the correlation between parent
07:33
and offspring for example but as it's

07:35
moved on it's changed a number of time
07:38
and we typically think of it now in
07:40
terms of specific coding regions of DNA
07:43
that code for a specific protein as sort
07:47
of what you call that kind of a
07:48
read-only version of it but but I think
07:51
that's what needs to be challenged and
07:52
there's this mismatch between the way
07:54
people think about population genetics
07:56
and heritability and how the definition
07:59
of gene has changed this is there's some
08:02
terrific papers about the history of the
08:04
term gene on PubMed but I think this is
08:08
largely forgotten and largely ignored
08:10
yeah I took the Greenmarket it's very
08:13
very important to understand that
08:14
there's an extremely important
08:15
conceptual difference here because as
08:18
Johansson introduced the definition in
08:20
1909 he referred to it as anything that
08:25
determines the phenotype I need fuss
08:27
anything now that is necessarily the
08:31
cause of the phenotype because that's
08:33
how it's defined there's no question you
08:35
can't do an experiment to find out
08:36
whether it is the cause no experiment
08:39
could demonstrate given that it's a
08:41
definition that is incorrect by contrast

08:44
if you define gene as a strip of DNA
08:47
it's a very important empirical question
08:49
for you and me and others to determine
08:51
does this particular bit of DNA actually
08:54
affect the phenotype now very
08:56
interesting this because if in for
08:59
example yeast you go through as
09:01
Hillenmeyer and his colleagues did in
09:03
2008 all 6,000 genes doing single
09:06
knockouts of each of them how many of
09:08
them produced an effect in normal
09:10
physiological circumstances only 20% 80%
09:13
are
09:14
it doesn't mean to say they're not
09:16
functional it means that the
09:18
physiological processes that determine
09:21
function represent function are
09:24
buffering those knock out so even if
09:27
that particular gene or its protein was
09:30
contributing a major amount of function
09:32
by virtue of the buffering in the
09:35
physiological networks you don't see it
09:37
and the complement refining your dentist
09:39
is if you look at the genome-wide
09:41
Association studies for common diseases
09:43
at the hub at the beginning of the human
09:45
genome project that there was something
09:47
called the common disease common variant

09:49
hypothesis and the idea was for things
09:52
like diabetes heart disease most cancers
09:53
you'd find a limited number of gene
09:55
variants that would put people at three
09:57
four five six fold risk for developing a
10:00
given phenotype and in fact for almost
10:03
everything that's been studied hundreds
10:05
of variants have been found they have
10:07
very very small effect sizes and the
10:09
vast majority are less than 1.5 but
10:13
let's maybe just yeah pick this up a bit
10:15
you know with the other side in terms of
10:17
what they might say here but you know
10:19
the gene phenotype blinkin disease has
10:21
been a big push with with funding in the
10:22
last last twenty years or so but surely
10:25
undeniably there are very strong genetic
10:27
links to disease if you know if you look
10:29
at Huntington's disease cystic fibrosis
10:31
breast cancer cardiac arrhythmias you
10:35
can pinpoint down to the molecular level
10:37
where this may have an impact on
10:39
phenotypes so yeah and that's true in
10:42
the sense of diseases with clear
10:44
patterns of heritability many of which
10:47
have been discovered with more primitive
10:48
tools before you know easy sequencing
10:52
and ton of genomics centers but what's

10:55
interesting is that for things that used
10:57
to be described as a single disease
10:59
phenotype for cystic fibrosis it turns
11:01
out now there are far more than then
11:03
single snippets or single variants that
11:06
account for it one that 5:08 mutation
11:08
counts for about seventy eighty percent
11:09
but twenty or thirty percent of cystic
11:12
fibrosis is explained by other variants
11:14
in the CFTR protein and they're finding
11:17
that the penetrance is is is less than
11:20
they had anticipated not a hundred
11:22
percent and also
11:26
that the the phenotype is highly
11:28
variable and a really interesting
11:30
example is the issue of sudden death in
11:32
young athletes initially if they thought
11:34
they'd be able to find some fairly
11:36
common things in the cardiac conduction
11:37
system but I think they found about
11:41
2,000 private mutations that run in
11:43
families that are responsible for this
11:46
and what's amazing is one individual in
11:49
the family may die the gene variant may
11:52
be present may be present and other
11:54
family members who have absolutely
11:56
normal
11:57
EKGs have no history of sudden death or

11:59
a arrhythmia so even if one member of
12:01
the family has the the sort of tragic
12:04
variant having another member of the
12:06
family where the same variant isn't
12:08
necessarily a death sentence so things
12:10
have gotten even more complicated for
12:12
simple diseases with clear patterns of
12:14
inheritance versus these very
12:15
complicated things like heart disease
12:18
diabetes most cancers could I try and
12:21
clarify something here David because I
12:23
totally agree with what mike has said
12:25
but I do want to make sure that we don't
12:28
give the impression that anybody thinks
12:31
the sequencing the genome was a mistake
12:33
yeah and I want to say something here
12:36
that I don't think is particularly
12:38
controversial because even craig Venter
12:40
and Collins have agreed with what I'm
12:43
going to say the outcome for healthcare
12:47
has indeed been disappointingly small
12:49
they say that not me however the outcome
12:53
for fundamental biology in particular
12:57
for understanding evolutionary biology
13:00
comparative genomics and for
13:03
reconstructing the trees even
13:06
identifying whole domains of life that
13:09
we didn't formally think was separate

13:11
like the archaea that are different from
13:13
the bacteria and different from the
13:16
eukaryotes
13:16
all of that has depended on comparative
13:19
genome sequencing so this is not an anti
13:21
genome sequencing session by any means
13:24
what it is I think he's saying two
13:27
things first of all that as Mike says
13:30
the results and as Venter and and
13:33
Collins also have said admitted in a
13:35
nature article in 2010
13:37
the outcome for health care has been
13:39
disappointingly small and the need for
13:43
physiological investigation to interpret
13:45
it is therefore vastly greater than we
13:48
ever thought and that's why I would say
13:51
that we now see physiology coming back
13:54
onto center stage because the only way
13:56
forward now is for physiology to come
13:58
back as the prince and the Golden
14:01
Slipper has got to be found David right
14:03
so so did David historically if you
14:06
think about a two dentists are these
14:07
things called clinical research units or
14:09
metabolic wards in hospitals where
14:11
patients with unusual diseases many of
14:14
them frequently genetic we're studying
14:16
in great detail with tremendous

14:18
phenotyping and those helped people
14:20
really understand key metabolic pathways
14:24
key patterns of inheritance other things
14:26
about physiological regulation and
14:28
dysregulation so at some level the older
14:32
marriage of detailed mechanistic
14:34
hypothesis driven phenotyping with
14:37
people with with strange syndromes could
14:39
go much much farther now that they can
14:41
be genotyped and in products of the
14:44
genes and in you know the metabolomic so
14:46
forth can be added in complement to that
14:50
so we're at a position now where you
14:52
know billions of dollars have been
14:53
spared on this particular research train
14:58
that everyone is part of or has been a
15:01
part of and it's quite clear that
15:03
complex diseases you know it's been
15:05
disappointing in terms of what we've got
15:07
out at the other end so Dennis if we
15:10
could just maybe backtrack at you know
15:13
how did we get to this point
15:14
philosophically in terms of the the
15:17
cycle that we got into with funding and
15:20
I think it's very important to
15:21
understand something that I think his
15:24
widely misunderstood in terms of what
15:27
the modern synthesis or the neo

15:29
Darwinist hypothesis just maybe explain
15:33
to the audience yes most people know
15:35
about Darwin but neo-darwinism and the
15:38
modern synthesis these probably are
15:39
unfamiliar terms indeed so and I'm going
15:41
to explain that that's right because
15:44
Darwin's theory of evolution was
15:47
actually a nuanced multi
15:50
factorial mechanism he specifically says
15:53
in the introduction to the Origin of
15:56
Species
15:56
I believe that natural selection has
15:59
been a major contribution but not the
16:02
only contribution to evolution moreover
16:06
in the Origin of Species he accepts
16:09
Lamarckism he accepts the inheritance of
16:11
acquired characteristics there are 12
16:13
places in the Origin of Species where
16:16
that is spelt out explicitly moreover he
16:19
even produced a theory for how it
16:21
happens he postulated that there were
16:24
particles he called him gemmules that go
16:27
down through the blood stream because of
16:28
course he realized that you have to then
16:30
explain how it can possibly be that
16:33
changes in the soma can have an effect
16:35
on the germline but that's precisely
16:38
what genome marking is so he was right

16:41
how do we get mislead now we got misled
16:43
by Vice Man August Weismann did an
16:46
experiment in which he claimed that
16:48
Lamarckism was impossible he cut the
16:50
tails off about six generations of mice
16:53
all the mice born to those animals had
16:57
tails on them now I want to say
17:00
something very important here that is
17:01
not a test for Lamarckism Lamarckism is
17:04
a test for the or testing Lamarckism
17:07
would be a test for whether if you alter
17:10
the environment not a mutilation of an
17:13
animal you get a functionally important
17:16
change in the inherited characteristics
17:19
so what you've got to do is to create an
17:21
environment if tail business is actually
17:24
important and he didn't do that of
17:25
course but then he went even further
17:27
he made the assumption it's an
17:29
assumption not a proof that all the
17:31
variations in the germ line were random
17:35
and small and that's what led to
17:37
neo-darwinism which is the such a theory
17:39
that accumulation of small random
17:43
variations with time and together with
17:46
natural selection can fully explain the
17:49
evolutionary process but there's no
17:50
proof of that

17:51
they never has been approved so the Neo
17:54
Darwinists got the causality the wrong
17:56
way around I'm afraid so yes the
17:58
causality is the other way round and
18:00
Barbara McClintock understood
18:03
that she did the first experiments that
18:06
showed that sections of DNA could where
18:09
she didn't call it DNA she didn't notice
18:10
DNA is 1942 she showed in corn that
18:14
sections of gin of DNA can move around
18:16
from one chromosome to another that's
18:19
the beginning of mobile genetic elements
18:21
she was stopped from publishing you
18:23
asked why as in where we got into the
18:25
mess we're in we got into the mess
18:26
because very powerful people actually
18:29
exerted their influence to stop
18:31
publication of important discoveries
18:35
which we should not have ignored Barbara
18:37
McClintock was one of the first 1953 on
18:39
what she never published on that again
18:41
because people didn't believe her what
18:43
happened
18:43
thirty years later 1983 she got the
18:47
Nobel Prize because by then of course
18:49
people understood that mobile genetic
18:51
elements were extremely important she
18:54
wrote in her Nobel Prize lecture the

18:57
genome is an organ of the cell the cell
19:01
to talk about causality is what tells
19:05
the genome what to do and that must be
19:06
the case because if I took the genome
19:08
out of a seven I put it in a petri dish
19:10
together as many neutrons as you like I
19:12
could keep it for ten thousand years it
19:14
would do absolutely nothing the genome
19:17
on its own is nothing the salmon it's
19:18
only is nothing you need two two
19:20
together and it's the cell that tells
19:22
the genome what to do so I think the
19:24
short answer David is we got the horse
19:28
before the cart or the cart before the
19:30
horse which that's the way round isn't
19:31
it yes cart in front of the horse yes
19:33
exactly so Mike might how do we square
19:37
all this but I think just to kind of add
19:40
to Dennis's riff there how many people
19:42
here have heard of Francis gaulden a few
19:46
Francis Galton was Darwin's cousin who
19:49
was a polymath independently wealthy who
19:51
attempted to mathematize Darwin and what
19:54
is he was one of the original
19:56
epidemiologist or bio matricies and
19:58
started making very simple heritability
20:00
calculations his students were Fisher
20:02
and Pearson so anybody who's ever

20:04
suffered through a statistics class can
20:06
blame Goldman
20:06
and as Galton is doing this Mendel has
20:11
rediscovered around 1900 and people and
20:14
then Johansen is Dennis mentioned in
20:16
nineteen
20:17
nine comes up with the idea of gene is
20:19
this sort of black box mechanism that
20:21
transmits phenotype and things are
20:23
racing along people come up with the
20:26
idea that the chromosomes versus
20:27
proteins or the genetic material and so
20:29
forth and how many people here know
20:32
about arrow and trade injure the famous
20:34
physicists trade injures cat so and I
20:37
didn't know this until I watch this
20:39
incredible YouTube video of Dennis
20:40
giving a talk in the Karolinska
20:42
Institute where he points out that that
20:45
that stranger was an Austrian I believe
20:48
yes yeah he was sitting out World War
20:51
two in Dublin he was a very interesting
20:52
man and he wrote a book gave a series of
20:55
lectures called what is life and he more
20:58
or less predicted the existence of DNA
21:00
as a crystal form and while as we were
21:04
talking about it at lunch here's a man
21:06
who really got into uncertainty and

21:08
helped us understand scientific
21:10
uncertainty but he developed this idea
21:12
that there was a read-only code actually
21:14
then more people got involved in that
21:17
Watson and Crick and come up with DNA
21:20
and then Crick comes up with something
21:23
called the central dogma of molecular
21:25
biology which says that DNA is really
21:27
DNA to protein as a read-only read-only
21:31
one-way street and they start using sort
21:34
of interesting terms dogma code breaking
21:37
the code blueprint of life and so forth
21:40
and before you know it you're you're at
21:42
a very hardcore position that genotype
21:44
equals phenotype genotype equals
21:47
phenotype now the nice thing about that
21:49
is that's very very easy to sell to
21:52
political leaders to industry to other
21:55
people who fund research because if you
21:57
break this code then you can do
22:00
something about it fix it I've called it
22:02
biological orthopedic surgery jeana's
22:04
broken find the fixed a broken gene cure
22:07
the patient but that's really the
22:09
narrative that's been sold it's been
22:11
really oversimplified and it's also a
22:13
narrative that is convenient for big
22:16
science moonshots as opposed to the

22:19
serendipity that has informed so much
22:21
biomedical research can I add something
22:23
about fudging it like if I made a
22:26
permission you see indeed hunting it was
22:29
absolutely right
22:30
in predicting that the genetic material
22:33
will be found to be what he called an a
22:35
periodic crystal which you think about
22:36
it is a very good description of a
22:38
polymer if you think the polymer is a
22:40
crystal which is a periodic because it
22:42
doesn't just go through a simple cycle
22:44
now that was his great success in what
22:47
his life published in 1942 but then he
22:50
made a website a catastrophic error
22:53
he said that physics and biology were
22:58
quite different because physics is order
23:01
at the level of thermodynamics from
23:04
disorder the bumping around of the
23:07
molecules down here but that biology was
23:10
order from order and you could see why
23:13
he would think that was the case and
23:15
that's the basis of genetic determinism
23:17
of course because since he thought it
23:19
was a determinate readout and a
23:23
read-only process you're led to that
23:27
conclusion but there is no way
23:29
absolutely no way in which biological

23:32
systems can be immune from the
23:35
stochasticity that occurs at a low level
23:37
what do you find when you take a
23:39
population of cells a cultured
23:42
population and you measure the
23:44
expression levels of a particular
23:46
protein it doesn't matter which protein
23:48
because they all show this you get a
23:50
huge variation in the expression level
23:52
between the different different cells it
23:54
can be three orders of magnitude
23:55
depending on the particular protein so
23:58
at the bottom level Schrodinger was
24:00
absolutely wrong there is stochasticity
24:03
in biology we all know that and it's
24:06
very important to take that into account
24:08
because when you come to the question of
24:10
whether the read-only view was or was
24:13
not not correct only if you could have a
24:16
determinate readout that was certain and
24:19
secure could you be safe in having that
24:22
kind of mechanism if you got
24:24
stochasticity you can't have that but
24:27
but you're not saying that genes are not
24:29
special dreams are they're special okay
24:32
Dave that's a very interesting question
24:34
they're special in the sense that they
24:37
are a special database they are not

24:40
special in the sense that they solely
24:42
determine the organism
24:44
tell you one little story in 2012 I was
24:46
asked to debate exactly this at a
24:48
congress of the is a conquest of systems
24:52
biology applied to cells I was asked to
24:54
debate with Sydney Brenner the great
24:56
Nobel Prize winner for his superb work
24:57
on C elegans and the motion I was asked
25:01
to propose was but a G an organism is
25:04
not defined by its genome Sydney was
25:07
asked to oppose that and he agreed at
25:10
dinner the evening before the debate I
25:12
said to him after we'd had some good
25:14
discussion over a glass of two of wine
25:16
but Sydney I can't understand why you're
25:18
opposing me because everything you say
25:20
is what I would say too he leant over to
25:23
many said Dennis I'm going to concede
25:32
and she did and I had exactly the same
25:37
experience with damned Annette many of
25:40
you here in the United States will know
25:41
Dan Dannette is one of the great
25:43
philosophers of this country you've got
25:45
some very great philosophers too but for
25:47
some reason or another he was trapped by
25:50
the Dawkins view of The Selfish Gene we
25:52
were to Congress together I gave a

25:54
lecture the day before he gave a lecture
25:57
he was writing furiously notes while I
26:00
was giving my lecture the next morning
26:02
he got up and said I've changed my
26:04
lecture you know what I think has
26:07
happened is very interesting
26:10
The Sitter duel that is neo-darwinism is
26:14
a house of cards
26:16
the reason is nobody here to debate with
26:18
us David is precisely that nobody has
26:22
done can do there's been no answer to
26:26
the chafe is your issue there's been no
26:27
answer to what I said in the mark in the
26:30
music of life a message has gone up
26:32
there and nobody's replied I don't think
26:33
anybody's there but the trouble is but
26:39
not there's a problem and have problem
26:40
for you and for me because the great
26:43
majority of our colleagues don't realize
26:45
that the house of cards has fallen you
26:48
talk to the funding agencies and you
26:49
won't find the result you'd expect if
26:53
people fully understood what we've just
26:55
been saying in
26:56
it becomes a need to sort of feed the
26:57
beast so you set up you start doing big
26:59
science how many people know here know
27:02
who proposed the Human Genome Project

27:03
you think it was the NIH was the
27:06
Department of Energy the Department of
27:08
Energy wanted to do the Human Genome
27:10
Project because they wanted to find out
27:12
about radiation effects from Hiroshima
27:14
and Nagasaki they also wanted to patent
27:17
the genes to do all sorts of other
27:18
things and they proposed this in the
27:19
early 80s the NIH got wind of it and
27:22
then there was you know the traditional
27:24
kind of bureaucratic infighting about it
27:25
but their argument was that that only
27:28
the Department of Energy because they'd
27:30
run the big physics lab and the
27:31
accelerators and so forth and so on that
27:33
they have the skill sets to do this sort
27:35
of big science and and if you look at
27:38
from the very beginning of it you have
27:40
people like Leroy hood saying in 1992
27:42
that in the next 25 years we will learn
27:45
more about biology than we have in the
27:47
previous 2000 now the good news for dr.
27:49
hood is he has two years left so you
27:53
know if he has a strong finishing kick
27:54
he'll be okay but and in if you in a lot
27:59
of these individuals who are still
28:00
around denied that they ever made
28:01
genetic deterministic statements but if

28:04
you go back into the 1990s it's clearly
28:06
there it's clearly there Eric Lander who
28:08
runs the Broad Institute has said he
28:12
never supported the common disease
28:14
common variant hypothesis I can show you
28:16
papers from the 1990s where he says that
28:18
they anticipate finding a limited number
28:21
of variants that evoke four to six
28:24
percent four to six fold increases in
28:26
risk for common diseases so now there's
28:28
a bit of revisionist history going on as
28:30
well but these people made very very
28:32
hardcore published predictions that
28:38
really are genetic determinism where
28:40
they said well yeah there might be a bit
28:41
of an environmental influence Minh but
28:43
and you see a situation again where dr.
28:46
Collins when he's been asked about this
28:48
has said his job is not to apologize for
28:52
being an optimist so that the hundred
28:56
thousand genome that the UK won't the
28:58
fund at the moment waste of time or a
29:01
million here well it's interesting
29:03
because the precision measured medicine
29:06
initiative is actually something that is
29:08
pitched by the director the unites three
29:11
or four times previously you can
29:14
download slides of the 2004 version and

29:16
the 2009 version in various versions of
29:19
this so you know who knows if it'll work
29:22
but but in fairness to the other side
29:24
yeah you know if it's not you know ten
29:27
genomes or a hundred thousand genomes
29:28
what about the personalized genome you
29:31
know it is the variation within the
29:33
person that is you need to personalize
29:35
it for that genetic base so if you then
29:37
you get your medicine so if you look at
29:39
prediction of diabetes 62 pretty good
29:43
risk genes for diabetes have been
29:44
identified in gee wass how many people
29:48
think that a gene score gives you a
29:50
better predictive test and waist
29:52
circumference so the receiver operator
29:55
curve for sixty two genes is about point
29:58
six the receiver operator curve for
30:00
waist circumference is 0.7 for waist
30:03
circumference and three or four
30:04
questions it's about point eight for
30:06
waist circumference three or four
30:08
questions and a blood sugar it's point
30:10
nine which is about as good at clinical
30:12
test as you can get now the argument is
30:15
for cancers that they're going to be
30:17
able to do precision medicine and target
30:19
the cancer therapy the oncologists are

30:21
wonderful people I love them to death
30:23
they make a lot of business for us
30:25
clinically in anesthesia but they have
30:28
also learned to live on something called
30:33
progression free survival or tumor
30:36
responsiveness
30:37
they are very reluctant to publish
30:40
survival data did this treatment improve
30:43
survival what is being found by in with
30:46
many targeted not all there's been a few
30:48
examples like Gleevec but with many
30:50
targeted therapies is they get a good
30:52
initial response but tumors are multi
30:54
clonal and adapt to the chemotherapy or
30:57
the targeted therapy and come back later
30:59
so if you look at the trials of targeted
31:02
therapy you're talking about perhaps one
31:04
or two months extension of life in many
31:07
cases it's going to be very difficult to
31:09
design randomized clinical trials to
31:11
prove it there were efforts ten twenty
31:15
years ago to target chemotherapy before
31:17
they were targeted biologics and they
31:20
were never brought to randomized
31:21
clinical trial
31:22
because they just couldn't figure out
31:23
how to do it so there is is a lot of
31:26
Hope here a lot of hype but there are

31:30
poorly defined metrics there's this
31:32
issue of kind of whack-a-mole you you
31:36
maybe make the tumor regress but it
31:38
comes back another way or in another
31:40
form with a different clone so I think
31:41
that that people should do this I think
31:43
it should be tried but I think clear
31:46
metrics for success should be defined
31:48
and I think they should be you have to
31:51
do clinical trials that can kind of
31:53
prove how this therapy might or might
31:55
not work I think it's something to add
31:56
to that if I may
31:58
David which is I think a very positive
32:01
message both for this audience and for
32:03
the funding agencies you see the reason
32:06
why what you've described Mike is what
32:09
you might expect is that give or take a
32:12
bit with maybe twenty five thousand
32:14
defined genes in human genome the number
32:18
of possible interactions the number of
32:21
possible circuits that you could form
32:23
from 25,000 genes is ten to the
32:26
seventeen thousand there wouldn't be
32:30
enough time over the whole billions of
32:34
years of the evolution of life on earth
32:36
for nature to have explored more than a
32:38
tiny fraction of those so looking for

32:42
the tiny fraction that actually exists
32:44
is like looking for a needle in a
32:46
haystack the size of the universe so how
32:50
do we do it we do it as Jim black did it
32:53
when you discovered h2 receptors we do
32:55
it in the way that many other forms of
32:57
drugs were discovered even before the
33:00
sequencing of the human genome you drill
33:02
down from the level at which you do get
33:05
understanding which incidentally is
33:07
physiology again why physiology is back
33:10
on the center stage
33:11
we need the genomics we need the data
33:14
and we need the young people in this
33:16
audience I've seen several of them that
33:18
I know are doing excellent work on
33:20
correlating genomics with our theology
33:22
we need all of that but it has to be
33:25
done with insight that's exactly how Jim
33:28
Black got his Nobel Prize and I think
33:30
you would point out that at the level of
33:31
a bioassay it
33:33
that that that helps you resolve some of
33:35
these initial signal-to-noise issues and
33:39
helps you understand what to pursue
33:41
versus to purchase myself a random yes
33:44
versus that so I really think that's
33:46
that's a key point is to sort of find a

33:49
bioassay or find a model system and I
33:52
think we talked about it again at lunch
33:53
do we have any comparative physiology
33:57
left and if they are there are any of
33:59
them here yeah so there's a couple here
34:02
one of the things we're suffering from
34:04
is once you believe genotype equals
34:07
phenotype it's possible to make animal
34:09
models where genotype a does in fact may
34:11
equal phenotype and one of the problems
34:14
the drug companies have had for example
34:15
is something like Alzheimer's diseases
34:17
they've created a bunch of models that
34:19
overexpress amyloid or tau the animals
34:22
get something that looks likes
34:23
Alzheimer's disease they then create
34:25
drugs that cure the disease in animals
34:27
that fail in clinical trials because
34:29
there's a whole prodrome of vascular and
34:33
other things going on in Alzheimer's
34:34
prior to the build-up of amyloid and
34:37
talent plaque so the epidemiology tells
34:40
you that vascular disease diabetes
34:41
hypertension and so forth are important
34:43
but the animal models have now jumped to
34:46
amyloid and tau so I think we need to
34:49
kind of go back to August curl 101 and
34:52
start looking for the right animal

34:53
models there's been tremendous recent
34:56
hits or successes looking at animals
35:00
that hibernate to think about
35:01
osteoporosis for example the the
35:07
constrictor snakes eating things that
35:10
having cardiac remodelling as a result
35:12
may provide clues it would help us
35:14
remodel the hardened pathologic
35:16
conditions so I think the other thing we
35:18
have to think about is how do we move
35:20
beyond the so much reliance on a limited
35:26
number of animal models and indeed that
35:29
requires us as we go back to wild
35:31
populations right let me tell you that
35:34
one of the most important breaks with
35:36
neo-darwinism with the modern synthesis
35:39
was by Konrad Waddington who was the
35:42
originator of epigenetic
35:44
incidentally 1957 his book the strategy
35:47
of the jeans
35:48
Conrad Waddington demonstrated a way in
35:52
which you could induce and in an
35:54
environmentally induced functional
35:57
change in fruit flies and he could only
36:00
do that in a wild population it would
36:03
take too long to go through the genetic
36:05
reasons for that but the wild population
36:07
was absolutely necessary we do it in a

36:09
cloned population you can't do it so
36:12
even one of the most important
36:13
mechanisms of evolutionary change
36:16
determined by Waddington who
36:18
incidentally did the experiments that
36:19
vice Minh did not do he did not cut
36:22
tails off he did a functionally
36:24
important nudging if you want to call it
36:27
that by the environment looking for
36:29
plasticity that was already in the
36:31
population that's where the animal
36:34
physiologist were coming very very
36:35
useful to us and we would not be able to
36:38
do that if we just worked on cloned
36:40
population so that the parallel is a
36:42
recent experiment or a series of
36:45
experiments on caloric restriction
36:46
Clarke restriction extends life and mice
36:49
correct that's been tried in 60 strains
36:53
have commonly used laboratory mice about
36:56
20 show no change in their lifespan
36:59
about 20 show an increase in lifespan
37:01
and about 20 show a decrease in lifespan
37:03
so it's really strange specific it's
37:06
also dependent on the sex of the animal
37:09
within each train so you get divergent
37:11
responses males versus females in the
37:13
same strain more importantly if you got

37:15
and capture wild rice or while twice
37:17
wild mice George I spent too much time
37:20
in Minnesota where we do get some wild
37:21
rice you capture wild mice and subject
37:26
them to caloric restriction they don't
37:28
live as long so again we need to start
37:31
thinking about animal diversity the
37:33
classic large animal models are
37:36
disappearing and we've really kind of
37:39
bet the farm on rodents and you wonder
37:44
about a lot of things related to that
37:46
and if we should go back to sort of the
37:48
August Krogh each problems got a got an
37:50
answer in nature if you can write find
37:52
the right model so you know I think it's
37:55
quite clear the
37:56
Dennis you've had an impact on sydney
37:59
brenner sure and I'm damned in it and
38:02
not yet Richard Dawkins no we'll come on
38:05
to Richard in the moon this is Oxford
38:08
talk here oh it's but you know certainly
38:11
Sydney you know has when you read some
38:16
of his statements you know in terms of
38:17
what he probably calls the b-52
38:20
approached unloading to find the answer
38:24
which I think he was quoted as saying
38:25
well or all of this big genome stuff low
38:30
input high-throughput no output quota so

38:37
well but he also invented exactly what I
38:39
was talking about in the drilling down
38:41
approach to find the needle in the
38:43
haystack he called it the middle out
38:44
approach that's in the Novartis
38:47
foundation symposium on the limits of
38:49
reductionism published in 1998 let's
38:53
just touched on Richard Dawkins for a
38:54
moment because many people in this
38:55
audience of course will be familiar with
38:57
this book The Selfish Gene and having it
39:01
having having experienced demand
39:03
firsthand as a student at Oxford
39:05
although we didn't see him much because
39:07
he's busy writing his books but you know
39:09
clearly can a gene be selfish Dennis
39:13
you can't attribute such a
39:16
characteristic to a sequence of DNA you
39:19
know when you first published The
39:21
Selfish Gene in 1976 it was a famous
39:25
philosopher so Anthony Kenny the put
39:28
League obvious question to him he said
39:30
Richard you know if all I knew as an
39:34
English reader or speaker was just the
39:37
letters of the English alphabet
39:39
I would not thereby be qualified to say
39:42
that I could understand Shakespeare he
39:45
got the point a sequence does not have

39:48
meaning except in a context Richard
39:52
Dawkins response was well I'm not a
39:56
philosopher I'm a scientist
39:59
I'm only interested in truth that was
40:03
1976 the year of the publication of the
40:05
surface gene I was chairing that
40:07
debate and that's when he lost me
40:10
because what he clearly doesn't
40:12
understand is that he is misused a
40:16
metaphor now I can prove that because in
40:20
1982 he was challenged by the
40:23
philosopher Mary Mitchell II who wrote a
40:25
criticism of The Selfish Gene and she
40:28
referred in passing to this metaphor The
40:30
Selfish Gene Richard wrote back article
40:34
in philosophy in nineteen eighty-two go
40:36
and check it that was no metaphor and
40:42
then he went on provided that you define
40:48
words in the way in which they are now
40:51
used by biologists now what is a
40:53
metaphor a metaphor is precisely a
40:57
change in the meaning of a word in order
41:00
to apply the concept to a different
41:03
target in your language I'm afraid it's
41:08
totally confused he's a brilliant writer
41:10
The Selfish Gene is a fantastic read so
41:13
a lot of his other books but he is
41:16
philosophically naive and I'm afraid his

41:18
misled us
41:19
misled many people for a very
41:22
considerable period of time
41:23
if you won't chapter and verse on that
41:25
it's in my little book the music of life
41:27
and if that's another thing I talked
41:30
earlier about how these sort of linear
41:32
narratives are easy to sell to quote
41:35
members of the establishment who build
41:37
universities who fund universities who
41:39
fund labs who elected officials people
41:42
in philanthropy people sometimes in in
41:45
commercial interests interested in
41:47
biomedical things and that's another
41:49
example of something that they could
41:51
latch on to could be explained to them
41:52
in a very simple way because it as you
41:55
pointed out it's become widely adopted
41:58
by behavioral economics people political
42:01
economics political science and law
42:03
sociology goodness me the whole range
42:06
the whole gamut of the humanities and
42:08
social sciences are bought into its that
42:10
is the situation the mixed metaphor so
42:12
yes so I think this would be a good time
42:15
just looking at time because we're
42:17
actually standing between you and your
42:19
society

42:22
but I think would be very helpful
42:24
especially if any of the opposition is
42:26
here that we can get some questions some
42:31
Q&A going between Dennis Mike and
42:34
yourself so the microphone is there
42:38
please come up and identify yourself and
42:41
let let's have some questions thank you
42:47
very much Jake Paulson from Preston and
42:48
UK we have spent a long time on a lot of
42:52
money and understanding the human
42:53
general and as you said very little
42:56
output out of this in terms of treatment
42:59
but what about some other diseases we
43:02
have with lifestyle changes where more
43:04
people die because a lifetime lifestyle
43:07
changes diabetes heart disease many
43:09
other why don't we spend more time in
43:11
trying to treat these understand these
43:14
more entreaties and prevent these and
43:16
all that one who spend on you one
43:17
general so if you look at you know from
43:20
1850 to 1950 death from infectious
43:23
disease or 1940 fell about 90% that was
43:27
before the development of antibiotics
43:28
and most vaccines Madu to public health
43:33
measures it fell to due to changes in
43:34
the built environment and there's a
43:36
whole collection of reasons that it fell

43:38
but they were all primarily social
43:41
policy and so forth and it's a it's it's
43:45
much easier to I think to sell people
43:47
the idea that if we know your genome
43:50
this sort of biological orthopedic
43:51
surgery I mentioned it's much easier to
43:53
sell that than it is to tell people you
43:55
you might have to have a serious
43:57
conversation about how car friendly
43:59
cities are you might have to have a
44:01
serious conversation about sugar
44:04
sweetened beverages that you might have
44:06
to have do for many things what we've
44:08
done with tobacco control so I think
44:10
that those are very politically
44:12
difficult things to do but in places
44:15
where the built environment has been
44:16
changed those diseases are much less
44:20
known there's excellent examples people
44:22
that ride their bike to work in
44:23
Amsterdam and Copenhagen live four or
44:25
five years longer then they're there
44:27
their neighbors who drive in in you know
44:30
you see people in most countries smoking
44:32
cigarettes while they're riding their
44:33
bikes
44:34
so they they may get lung cancer but
44:36
they're at least protected from the

44:37
diabetes so I think that that you know
44:40
and you get into discussions about the
44:42
nanny state and so forth and so on but
44:44
traditionally public health measures
44:46
have the return on investment has been
44:50
huge in comparison to dealing with
44:53
diseases after they occur
45:01
hi I'm Fred lifts from Berlin I'd like
45:04
to ask the speakers for some personal
45:06
advice I was educated in medicine in the
45:11
1960s and I thought I did personalized
45:14
medicine because I would tell the
45:15
individuals that had a huge waist
45:18
circumference that maybe something could
45:20
be done about it and those that smoked I
45:21
asked them to stop but my friends PhDs
45:26
like Eric Lander or Detlef Gunton who is
45:32
an MD but doesn't have a license to
45:34
practice medicine now are coming up with
45:37
precision medicine and the cost of the
45:40
genome has plummeted from a hundred
45:42
million bucks to a thousand cheaper than
45:45
getting an MRI scan or a colonoscopy
45:47
and I'm certain that even within my
45:50
lifetime all people at birth instead of
45:52
having a guthrie test will get their
45:54
genome sequenced irrespective of the
45:57
advice that you give now what our

45:59
practicing physicians supposed to do
46:01
with this information well and Fred
46:04
that's really the problem is so you tell
46:06
somebody that they have a 1-point their
46:08
relative risk of developing disease X's
46:10
is 1.2 so you could say well why you
46:13
have a 20% increased risk of having this
46:16
disease on the other hand if it's a very
46:18
rare disease you know only a very
46:22
limited number of people may get it so
46:23
how you turn this information into
46:26
clinical decision making tools is almost
46:29
impossible and that's one of the main
46:32
problems and so if you actually look at
46:34
it using these larger phenotypic tests
46:38
are essentially are the clinicians
46:40
equivalent of a bio assay because they
46:43
tell you so much more in terms of risk
46:45
prediction but the expectations are
46:47
going to be massive because of the
46:49
propaganda that's made and our attorney
46:51
friends are going to be listening to
46:52
this well and so if you if you look at
46:54
it exactly so there's a couple of
46:55
interesting things there the studies
46:57
that have been done so far show that
47:00
most people don't understand the these
47:03
risk ideas risk estimates people

47:06
frequently who are told they're to
47:07
increased risk become Cavalier and think
47:10
there's nothing they can do about it
47:11
people who think that their reduced risk
47:13
think become
47:14
cavalier and think while I'm protected
47:16
you know so I can go and do whatever I
47:17
want and there's some evidence from
47:19
statin data people put on statins and
47:21
think they're vaccinated against heart
47:22
disease and they gain weight and their
47:23
behavior gets worse and if you look at
47:26
the if you look at the people who get
47:29
their gene sequence by by commercial
47:31
organizations you know mail-order genome
47:33
testing there is some evidence that
47:35
those individuals start demanding
47:37
biopsies they start demanding more and
47:39
more follow-up and there's an iatrogenic
47:42
cost to all of this so so until people
47:46
have a serious conversation about how
47:47
you interpret this data turn it into
47:49
clinical decision making tools and make
47:51
sure that it isn't just a license for
47:53
the medical industrial complex to do
47:55
more scans more biopsies more
47:57
exploratory surgery and so forth and so
47:58
on

47:59
you're not ahead so III agree with you
48:03
and that's why I've been trying to
48:04
promote an or sober discussion of some
48:06
of these things yes please God's way to
48:09
get belief from Thomas Jefferson
48:10
University it's very fascinating
48:13
discussion and one thing I want to bring
48:16
up for your comments as fellows those
48:18
might be in the audience is uh there
48:21
might be a thousand dollar genome but
48:23
there's actually a hundred dollar
48:24
bracelet Fitbit or whatever it is that
48:26
you wear that collects physiological
48:28
data of a whole battery of things so
48:30
there is an opportunity here that's much
48:33
more personalized than the thousand
48:35
dollar genome in ways that brings back
48:38
the conversation and the ability to
48:39
influence in a completely different
48:41
direction if you will and is that
48:43
something that we ought to be talking
48:46
about and incorporating in the way we do
48:48
research and not just it's a population
48:50
thing you know there are new tools that
48:53
would will permit people to phenotype
48:55
large numbers of individuals how
48:57
accurate that is how reliable it is so
49:00
forth and so on there's been some papers

49:01
in JAMA on those topics but but there is
49:05
some potential there but you know most
49:08
people buy their monitors use your
49:10
monitors for a while and only a limited
49:12
number really are enthusiasts for it but
49:16
could we add something here if we may
49:18
March I think is very relevant to this
49:20
very good question when I had a
49:23
conversation like this with the chief
49:26
scientific officer of 23andme
49:28
of course one of the major genome
49:30
sequencing companies she admitted you
49:33
needed precisely what you're saying that
49:35
is you've got to add the phenotypic
49:38
characteristics measured carefully to
49:41
the genome characteristics before you
49:43
can do anything that's the first point
49:45
so I think the genome sequencing people
49:50
possibly I mean the industry evolved
49:53
possibly led by the FDA which of course
49:56
has been very very concerned about
49:58
precisely this question there's some
50:00
very big ethical issues here which I'll
50:02
come to in just a moment they actually
50:05
now recognize that you'd need to have
50:07
both right that's the first point now
50:09
the second thing to say is there are no
50:10
good and bad genes there are genes that

50:14
are used
50:16
now remember cystic fibrosis remember
50:21
the that the sickle cell anemia -
50:26
usually through the evolutionary process
50:29
because remember we're supposed to be a
50:31
conversation about evolution as well
50:33
there are reasons why those genes are
50:36
there and they have to be positive
50:39
reasons for them had to have been
50:41
selected so I'd like to get the message
50:44
across that this is going to be
50:46
ethically quite difficult some of those
50:50
genes that we identify their alleles of
50:53
course those genes variants as those
50:55
genes as being risk factors may or may
50:58
not be overall risk factors until you
51:01
know what else they do and where'd you
51:03
get that information from again you get
51:05
it from Physiology drilling down to find
51:08
out function that's again why we are
51:10
necessary people who are heterozygous
51:12
for cystic fibrosis the ideas might have
51:14
been protected against cholera many many
51:16
years ago yeah and and and with the
51:19
sickle cell trait not sickle cell
51:22
carriers may be protected from malaria
51:24
exactly there's a number of examples of
51:26
things like that ideas about salt

51:29
retention being helpful in in in in hot
51:34
humid environments for survival and in
51:37
keeping our blood pressure up and
51:38
keeping our blood volume up but then you
51:40
put people in a
51:41
low physical activity salt filled world
51:45
and they become hypertensive I mean
51:47
those that's those are
51:48
oversimplifications but but but those
51:50
are some of the ideas that are out there
51:52
so a question about John Horne from the
52:03
University of Pittsburgh first of all I
52:04
want to say this is wonderful I think a
52:07
big problem we're having here I think
52:09
we're all in agreement so we're sort of
52:10
preaching to the choir and one of the
52:13
problems in listening to this is that
52:16
there's a big difference between the
52:19
scientific opportunity that genomics
52:21
presents and and our opportunity to
52:24
translate that into better Public Health
52:26
and I think in some ways what's
52:29
happening in this country is a repeat of
52:32
what happened during the doubling of the
52:34
NIH budget 15 years ago where
52:36
essentially when we were guilty of this
52:39
to some extent that we oversold it to
52:42
the government and to the public well

52:44
what the doubling of the budget would
52:46
deliver and at the same time
52:49
now what genomics will deliver I think
52:53
it will eventually deliver but instead
52:55
of happening in a framework of ten years
52:57
we might be looking at something that's
52:59
50 or a hundred years away and there'll
53:01
be many surprises and but the problem we
53:05
have is really a political problem in
53:07
the sense that the train has left the
53:09
station the President of the United
53:11
States is already endorsed personalized
53:13
medicine many of our home institutions
53:16
are busy constructing genomic
53:18
personalized medicine Institute's as
53:20
fast as they hand our Dean's are
53:22
funneling money into it as fast as they
53:24
can and everybody wants to make this
53:28
happen at their place so I think the
53:31
challenge for physiology is to figure
53:34
out how we can constructively moderate
53:37
and modulate that discussion so that it
53:40
doesn't turn into an even larger
53:42
political disaster
53:43
well could I say something about that
53:47
news I've had considerable experience of
53:50
advising government committee
53:52
and research agencies certainly in the

53:55
united kingdom and i think you're
53:58
putting a finger on a very major
53:59
difficulty of course the great majority
54:02
of the people were talking to educated
54:05
in biology 30 or 40 years ago
54:07
and they really have no idea of the sea
54:11
change has occurred and that's why it's
54:14
referring earlier on to the fact that
54:15
the house of cards the citadel if you
54:17
like is empty but many people still
54:21
don't know that now i think you're
54:24
absolutely right whatever we do we must
54:27
not make undeliverable promises and i
54:30
have a big worry here because there are
54:33
many amongst our colleagues even outside
54:36
the community of physiology who have
54:39
thought that well the answer to why
54:41
things went wrong or went wrong in
54:43
relation to health care anyway and not
54:46
in relation to use for fundamental
54:48
biology as i said earlier on the
54:50
comparative genomics has been extremely
54:52
valuable but what they would say went
54:55
wrong with genomics in relation to
54:57
health care can be solved and it can be
55:00
solved by a field called systems biology
55:03
now i always ask myself the question
55:06
when that became popular from about the

55:10
year 2000 why invent a new word actually
55:15
a city Brenner's view - you've got a
55:17
word for this already is physiology so
55:21
we don't in a sense need well but bill
55:24
nevertheless understand the politics
55:26
here it is that of course many of those
55:29
who come into the area of realizing that
55:32
a systems approach is needed are not
55:34
themselves
55:34
classically physiologist and I welcome
55:37
that that's absolutely great but I think
55:40
we're arguing here for hearts and minds
55:43
because it's quite a small proportion of
55:46
systems biology that is actually
55:48
understanding the role and the
55:51
significance of physiology may be
55:54
something may be something
55:56
maybe some okay I continue even if the
55:59
gods do whatever so so let me just let
56:05
me let me add one more thing if I could
56:07
didn't Dennis and David I I think I
56:10
would encourage everybody to go and read
56:12
calm rowing drips oh yes the
56:15
spectroscope yeah I'm and there's a
56:17
shorter version of it about the
56:18
discoveries required to do open-heart
56:20
surgery it's in circulation research in
56:22
about 74 or 75 and it's much easier to

56:26
sell these linear stories to the
56:28
agencies to the funders we're going to
56:30
make a lot of progress we double the NIH
56:32
budget or if we have a war on cancer
56:33
there's a quote in there from Lyndon
56:36
Johnson about we must not let cures be
56:39
locked up in the laboratory from 1966
56:42
you can look at these quotes of Lyndon
56:43
Johnson and in there in the calm row and
56:46
Rip's paper change a few words and you
56:49
could just have Barack Obama be seeing
56:50
them right now so it's really really
56:53
instructive and I think one of the
56:54
things again that's hard to explain to
56:56
people is how we need to make kind of
56:58
Yogi said we made the wrong mistakes
57:00
that's why we lost the baseball game we
57:02
have to make the right mistakes nitric
57:04
oxide was a mistake viagra is a mistake
57:06
veg F inhibitors were gonna cure cancer
57:08
they're great for macular degeneration
57:10
they don't do much for cancer Remicade
57:12
terrific for arthritis doesn't do much
57:15
for sepsis what it was what it was
57:18
created for so trying to help people
57:21
understand the serendipity the things
57:23
that might come fifty or a hundred years
57:24
from now you know these people won't be

57:27
running for office then so given that
57:30
we've run out of tokens on the light
57:32
meter yeah the tennis courts yeah and
57:37
but I think have we really got back to
57:40
sort of my introduction about the prince
57:42
and the princess the Cinderella
57:44
subject in fact physiology really does
57:48
need to reclaim that slipper and
57:52
hopefully this conversation has has
57:56
given you a bit of firepower to think
57:57
about what's being said I'm very
58:00
grateful and on your behalf would like
58:02
to thank Mike and Dennis and at the end
58:08
of
58:09
the hall there are complimentary copies
58:12
of the special issue on physiology and
58:16
evolutionary biology so thank you very
58:18
much for coming