PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

East Midlands RSN NEWS

from the East Midlands Research Support Network

****** March 2014 / No 14 ******

Welcome to this edition of RSN News.

Our thanks to Brian Turner, who was the first to respond to our request for readers' input for the 'Has this been researched?' feature, with a query as to whether iron could be a trigger in causing Parkinson's. The results of our information research appear in this edition.

(Pills, by koratmember: freedigitalphotos.net)

Professor Roger Barker gave a very interesting talk on gene therapy at Newark, which was also presented very clearly and readily understandable by lay people. The report on his presentation also appears in this edition.

The next meeting of the East Midlands RSN Steering Group will be on Tuesday 15th April at Newark. For full details, see 'Coming Up' on page 7. Anyone who would like to come to this or any other Steering Group meeting is very welcome. You do not have to be a Steering Group member to participate and no scientific or research experience is required. All you need is an interest in actively helping to make research accessible to people living with Parkinson's in the East Midlands.

Inside this issue:

… and much more!

(Online news, by renjith krishnan: freedigitalphotos.net)

If you are interested please come along, and if you would like papers before the meeting please email our Secretary, Lionel Paulo.

We hope to see you soon.

Ian Billcliff, Editor

(Teamwork and success, by renjith krishnan: freedigitalphotos.net)

News & Events

Research Meeting at Newark branch on 17 February:

The Future Treatment of Parkinson's disease

Dr Roger Barker, Department of Clinical Neurosciences, University of Cambridge

An amazing 90 people turned up to hear Dr Roger Barker speak on this topic and were not disappointed. His was an exceptionally clear account of several lines of potential therapy for Parkinson's disease. But it was necessary to start with some basic facts about the nature of the disease and also why it is important to recognise that not all Parkinson's is the same.

We all know that everyone's Parkinson's disease is different. But a study of all the new cases arising in Cambridgeshire over recent years has revealed that, from the point of view of the neurologist, there are broadly two types, that call for two different types of treatment. Characteristic of the first type is an age at diagnosis of over 72 years, coupled with early cognitive problems. It is a sad but common observation that people in this category tend swiftly to develop a range of

symptoms, both mental and physical, that go beyond the characteristic Parkinson's ones of tremor, stiffness and slowness of movement.

The second type, predominantly with younger onset, has the characteristic motor symptoms of Parkinson's but they tend to remain relatively stable for perhaps many years.

It is only part of the story to say that Parkinson's is due to the dopamine-producing part of the brain. Other parts of the nervous system are also affected and this is particularly the case for patients of the first type. For the second type, replacement of dopamine in one way or another can be very effective. But for the first type, dopamine drugs do not adequately address symptoms like dementia, walking problems, hallucinations and so forth; they become increasingly troublesome even after tremor and stiffness are reduced by the most carefully tuned dopamine-replacement therapy.

Dr Barker described a number of trials involving the transplantation of foetal neural cells to replace the dopamine cells lost. Some patients experienced great improvement, occasionally being able to come off medication altogether. Others, however, developed severe dyskinesia. Another set of trials, however, led to the conclusion that the transplants were no more effective on average than sham transplant operations on patients. Yet the TRANSEURO group, led by Dr Barker, decided to persist in this line of research because, first, certain individuals clearly benefited from transplants and second, there were several possible reasons why the trials gave negative results, one being that patients who were most likely to display negative outcomes – ie the patients of the first type described above - were not filtered out beforehand. New trials starting in March 2014 will pay particular attention to (i) better patient selection, (ii) optimised collection of foetal cells and (iii) optimised delivery of the cells to the brain.

(dna, by dream designs: freedigitalphotos.net)

Foetal cell transplantation is expected to produce proof of principle, but is unlikely to become widely practised. This is because the development of neural stem cells is expected to mature over the next decade and there are good reasons why these should be used instead.

Dr Barker also described a couple of other potential treatments which, again, would be of greater benefit for patients of the second type where dopamine replacement therapy is effective at restoring quality of life.

The first is a gene therapy named Prosavin, which introduces a gene into the brain which produces dopamine where it is needed.

The second is the use of a chemical substance called GDNF – glial cell derived neurotrophic factor. Hopes are, with some believable evidence, that GDNF is able to restore damaged brain when it is infused into that part where dopamine cells have been lost. Quite a complicated story surrounds GDNF research, which again involves initial

promising results being overtaken by negative ones. Yet, again, some sustainable reasons have emerged that could explain the failures and new trials have been started by Stephen Gill's team in Bristol.

So for the people with Parkinson's of the second type, for whom dopamine replacement therapy works pretty well, there are plenty of hopeful developments. But there are other lines of investigation that could help those patients of type one, where what is needed is something to slow down or stop the progress of the disease in all the different parts of the nervous system where the pathology exists.

Dr Barker explained that around fifteen years ago it was discovered that a particular ubiquitous protein called alpha-synuclein was at the heart of the disease, because its molecules can misfold and eventually aggregate together to form the major part of the insoluble bodies in nerve cells discovered many years ago by Lewy in Parkinson's patients. Research over only the last few years has shown that this misfolded protein (a) is found in many parts of the nervous system outside of the brain and (b) seems to appear first in the nerves of the gut and the olfactory bulb. Not only that, but it spreads along the nerves in a way reminiscent of prion disease, where a misfolded protein molecule can act as a template to induce other normal protein molecules to misfold too. This is why it is said that people have probably had Parkinson's for ten years before they are diagnosed, because it could be that it takes that long to reach the dopamine-producing cells and destroy half of them to produce the characteristic Parkinson's symptoms.

(Stamp showing toxic word, by stuart miles: freedigitalphotos.net)

So maybe the pathology of Parkinson's is kicked off in the gut by an ingested toxin. This has brought researchers round to thinking about whether there is a way of removing the misfolded alpha-synuclein to stop the prion-like chain reaction so that it can do no more damage. Work is now going on to see whether anti-bodies can be developed. Maybe in future there will be a vaccination against Parkinson's, particularly for those at especial risk.

As you can guess, Dr Barker spoke in fascinating detail, only the bare bones of which are recorded here. There is little wonder about why he is in demand as a speaker. He addressed the World Parkinson's Congress in Montreal and covered a lot of the same material as at Newark. The video recording has now been put up on the web and you can view it, with all the slides, at http://www.icastpro.ca/events/wpc/2013/10/04/3rd-world-parkinson-congress/play/1694 (You may have to register but it is free.)

John Telford

** A very interesting book entitled "Monkeys in the Middle" by Nick Nelson, which covers the history of GDNF prior to this latest trial, has been brought to our attention by Bob Raeburn. - Ed.*

Melatonin Hypothesis

Following the article on this subject in our February edition, Harry Pearman has drawn our attention to a recently published paper giving the results of some further research on the topic. This may be viewed at: http://www.ncbi.nlm.nih.gov/pubmed/24566763

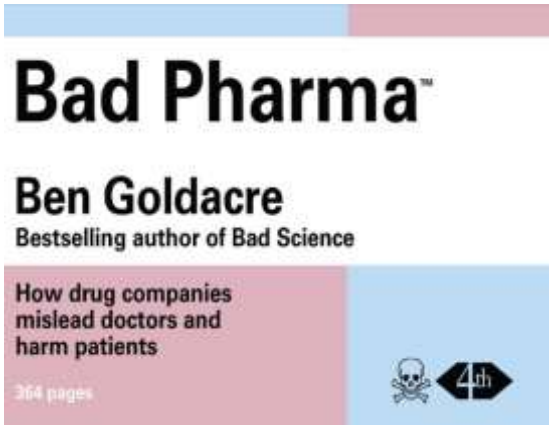
Good News for www.alltrials.net

There was good news to start the year for the Alltrials organisation. Johnson & Johnson, the pharmaceutical giant has signed up to their campaign.

The Background

In March last year we reported that Alltrials, led by Ben Goldacre, author of *Bad Pharma,* was campaigning for legislation to require all clinical trials to be registered and for ALL the results of such trials, past, present and future, to be made publicly available. *Bad Pharma* had revealed that, although many trials need official approval and should be registered, there is, at present, no legal obligation to publish the results. So, in many cases only partial information on the history, side effects and likely efficacy of drugs is available to those who are prescribing or using them. In general, trials with positive outcomes are more likely to be published than those with negative reports.

It is not difficult to understand why this happens. On the business pages of The Sunday Times of 9 February 2014 there is an interview with Sir Andrew Witty, the CEO of GlaxoSmithKline, which was one of the first major pharmaceutical companies to sign up to the Alltrials campaign. In passing, the article mentions that, according to the investment bank Berenberg, "Glaxo has managed a success rate of only 50% with data it has published on late stage trials of new drugs."



Progress

This does not look too good on the business pages, but from a different vantage point it indicates that negative results are now being published. So scientists can learn what doesn't work as well as what does. In the long run this must be good for science.

Although they have expressed support for Alltrials, GSK are still managing their own response to requests for information on their trials, but Johnson & Johnson have gone a step further. They have agreed in principle that all their data should be available, but, in order to ensure it is used responsibly, the company has engaged the Yale Open Data Access Project to manage and respond to requests for information. It will be up to this independent body, not to J&J, to decide whether the request for information is legitimate and should receive a positive response.

Others Join in

Following the example of GSK and J&J, a number of other large pharmaceutical companies have together launched an online portal where researchers can request access to

anonymised patient-level data on their clinical trials. All other industry, academic and non-profit trial sponsors are being urged to include their studies on the portal too. Such a resource will enable not only scientists, but also, in some cases, patients to make decisions following study of all previous work on particular topics.

Legislation Pending; Contact your MEP

Possibly doubting that voluntary agreements are sufficiently binding, the European Parliament is holding a debate on 2nd and 3rd April 2014 on legislation to require all clinical trials to be registered and their results published. Alltrials is urging its supporters to write to their MEP, asking them to vote for Clinical Trial Regulation. Alongside the increased transparency about registration and publicising results of trials, this regulation streamlines the currently cumbersome Europe-wide procedure for gaining ethics approval for clinical trials which cross national boundaries.

Meanwhile, in Westminster, the influential Public Accounts Committee has recommended that the Department of Medicines and Healthcare Regulatory Authority should take action to ensure that the full methods and results are available to doctors and researchers for all trials, on all uses, of all treatments currently being prescribed and should also ensure that there is clear and frequent audit of how much information is available and how much has been withheld.

Parkinson's UK

Rachel Evans, Clinical research and campaigns adviser for Parkinson's UK, confirms that our organisation is signed up to the Alltrials campaign and is following closely the progress of European Clinical Trials Regulation mentioned above. Terms and conditions of research funding by Parkinson's UK requires the registration of clinical trials and the publication of the results.

What you can do

Members of the RSN who want to support this drive towards sharing information, which will lead to "better science", should follow the Alltrials campaign on their website, where they can also find list of MEPs and a sample letter. http://www.alltrials.net/2014/one-last-hurdle-remaining-in-clinical-trial-reform-how-you-can-help/

Caroline Maxwell

Addendum:

Pharmaceutical companies and academic research institutions are not the only organisations to store and use medical data. Our own NHS has a vast archive of the medical histories of the UK population which it is proposing to collate for research and management purposes. The project is called Care.data and, as you are probably aware, has been beset by so many problems that implementation has been postponed at least until May 2014. At the end of February 2014 Ben Goldacre wrote 2 excellent articles on this topic in the Guardian:
http://www.theguardian.com/commentisfree/2014/feb/28/care-data-is-in-chaos
http://www.theguardian.com/society/2014/feb/21/nhs-plan-share-medical-data-save-lives

Goldacre continues to support the principle of sharing data, but laments the appalling lack of forethought and clarity concerning the implementation of the Care.data. He points out the importance of maintaining the trust of the public that their records will be used responsibly and he deplores recent misinformation by government bodies concerning the sharing of medical records that has already taken place. Readers commenting on his articles are mostly in favour of opting out of sharing their records but Goldacre is not ready to abandon hope just yet. He lays out steps the government should take and reminds us "Care.data needs to work: in medicine data saves lives."

We urge RSN members to read the articles and make up their own minds.

Caroline Maxwell

Coming Up ...

Sat 22 March 2014
10.30 am to 1.00 pm

East Midlands Researchers Meeting at Leicester University

The main purpose of this is for researchers to exchange information on their work on Parkinson's amongst themselves and to discuss areas of mutual interest. There will be a small audience of lay people, who will be present mainly to 'listen in' on the discussions. Some of the projects described will need more background knowledge to understand them than others and time constraints mean that a basic understanding of Parkinson's pathogenesis by attendees will be assumed. Some time, however, will be reserved for input from RSN members present.

If you wish to attend, please e-mail John Telford on jntelford@ntlworld.com or Ian Billcliff on imb248@outlook.com.

Tue 15 April 2014
12.00 to 3.30 pm

EMRSN Steering Group Meeting

at Holy Trinity Community Centre, Boundary Road, Newark NG24 4RU. If you would like to come along, please contact our Secretary, Lionel Paulo on ljpaulostk@talktalk.net

October 2014:

East Midlands RSN 3rd Annual Conference

Sun 2 November 2014

3rd National Research Supporters Day

Royal York Hotel, Station Parade, York
Bookings may be made from August, but you can register your interest by e-mailing researchevents@parkinsons.org.uk or phoning 0207 963 9356

Full information on events throughout the country can be found on the Parkinson's UK website, by visiting http://www.parkinsons.org.uk/researchevents

"Has this been researched?"

A question and answer forum on Parkinson's research

Just to remind everyone, this new feature opens up the newsletter to readers' input. You are invited to ask questions on any aspect of research or tell us about your personal experiences with, or concerns about, anything to do with research. This can be done anonymously if you wish. We will endeavour to find out answers about the topics raised, to be printed in future editions. Readers' responses and further comments are also invited for inclusion in future editions. Alternatively, we would welcome your own articles on topics that you have looked into yourself.

Questions or articles can be sent by e-mail to Ian Billcliff at imb248@outlook.com

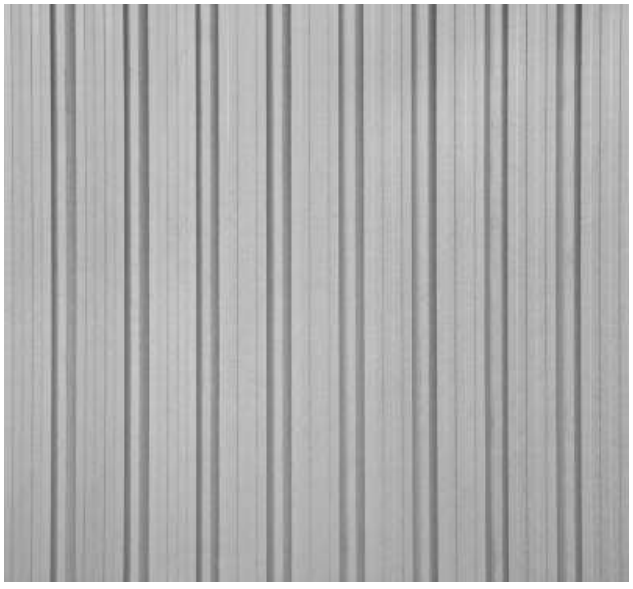
Iron and Parkinson's

An EMRSN News reader wrote in to say:

"I have seen recent articles on the role of iron in Parkinson's. Prior to being diagnosed, for about a year [my wife] was taking an over the counter iron supplement to counteract hair loss. Could this have been a trigger?"

Unfortunately, the quick answer to the question is "Who knows?" There is rarely any way of knowing what triggered the development of Parkinson's in a particular individual.

But all this begs the question of whether taking iron supplements increases the risk of developing Parkinson's. A scientific paper published a few years ago entitled "Dietary Iron Intake and Risk of Parkinson's Disease" [ref 1] throws some light on this. (It is in Pub Med Central so is free for you to read). In it you will find that there is no simple Yes or No answer. Broadly, they did not find that a high total intake of iron through diet and supplements produced a measurable increase in the risk of Parkinson's. Yet they did find a small increased risk in certain circumstances, these being that, first, the daily intake of iron was over twice the recommended daily allowance, second, that intake of vitamin C was low and, third, that the extra iron ingested was non-heme i.e. from non-animal sources. Even then the risk was only increased by less than a third – meaning that if now about 3 in every two hundred people over the age of 65 have Parkinson's, there would be about 4 if they ***all*** had had high iron/low vitamin C intake. Note that the risk was to people with *sustained* high dietary intake. So really the risk identified would appear to be very small, even in the most extreme cases.



(Metal background, by feelart: freedigitalphotos.net)

An associated question which can lead us to examine this topic more deeply is 'Why should anyone be on a high iron diet?' Clearly one reason to take iron supplements is that a doctor has diagnosed a medical condition that perhaps has led to iron deficiency that needs treatment. In such cases normal medical supervision should take account of risks of side

effects of all kinds, with medication being adjusted and continued for only so long as absolutely necessary.

Another reason for supplementation could be a person's own desire to have as beneficial a diet as possible. I am sure we can all quote examples where this has not always had beneficial outcomes and some companies pushing dietary supplements are not entirely blameless. The dividing line between 'medication' and 'nutrition' is blurred here and it is where caution must be advised, especially when statutory regulation of food supplements is difficult to design and impose.

The question above relates to iron supplements possibly ***triggering*** the development of Parkinson's. This implies a pre-existing propensity for developing the condition, which needs something to kick it off. Research has revealed that there could be an inadequacy in one of many systems that keep the body working properly. A lot of different genes have been found to be associated with Parkinson's which means that a variation in one or more could prime a person for developing the condition. Similarly, in some cases it appears that certain environmental factors – exposure to pesticides, lack of vitamin D and so on – could produce a vulnerabilty. A problem with the body's iron handling mechanism – possibly genetically caused - could also be a vulnerability that could tip over into Parkinson's in certain circumstances.

(Flowing blood cells, by Victor Habbick, freedigitalphotos.net)

Iron is vital for the functioning of the body. It is in haemoglobin in the blood cells, which enables the blood to carry oxygen around. It is also an essential constituent of mitochondria, the 'powerpacks' of every cell. Its vital properties relate to the fact that it can exist in two states, Fe^{2+} and Fe^{3+}, and going from one state to the other drives the essential oxidation and reduction reactions that are at the heart of energy production. Usually these iron ions are closely controlled and the energy transitions are carefully channelled. But if these ions become free, all sorts of damage can be done. Free radicals (molecules which have unpaired electrons) and other reactive oxygen species can be produced, which are damaging to cells and DNA.

$$\text{Substrate} + Fe^{2+} \leftrightarrow \text{Free Radical}^{\cdot} + Fe^{3+}$$

Mechanisms like this are involved in Parkinson's pathogenesis. Fortunately the cells usually mop up free iron very efficiently and even when there is a temporary increase in free iron, such as when an infection occurs, the iron is rapidly captured and 'sequestered' or packaged away. The dopamine-producing cells in the substantia nigra – those that are affected in Parkinson's - use a lot of energy even in normal times and have to work hard to keep down the oxidative stress produced as a consequence. If they fail, Parkinson's can result. Their last-ditch effort involves the removal of free iron and laying it down in insoluble deposits and these can be observed in Parkinsonian brains.

If you have got through the bit of science above and arrived here, you may be interested in more information on iron and Parkinson's. SPRING, which was a special interest group of Parkinson's UK that gave way to the RSN, held a conference on this topic in 2007 and some reports on what was covered there are given in reference 2 below.

John Telford

References:

1 *Logroscino, Giancarlo, Xiang Gao, Honglei Chen, Al Wing, and Alberto Ascherio. "Dietary Iron Intake and Risk of Parkinson's Disease." American Journal of Epidemiology 168, no. 12 (December 15, 2008): 1381–1388. doi:10.1093/aje/kwn273. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727188/*

2 *Reports from Iron and Parkinson's conference, January 2007: http://spring.parkinsons.org.uk/images/stories/SpringDigest/2007/43_10_IronConf.pdf*

Next Issues…

Just a few of the topics to be covered in the next few issues of RSN News:

News and Events
Report on the Researchers' Meeting in March

Has this been Researched?
Effect of hormones on PD
Relationship between jobs and risk pf developing PD
Pain and PD
Dyskinesia

Lionel's Lessons
Exercise - Parts 1 and 2

Personal Perspectives
R.I.P.E. – a really interesting article on exercise
JUNK – a personal insight into DNA

And much more ….

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EMRSN News is published monthly by the Steering Group of the East Midlands Research Support Network (RSN). The RSN brings together people driven to help find a cure and better treatments for Parkinson's. Through our network, anyone can get involved in research and raise funds and awareness for Parkinson's research.

The views expressed EMRSN News are not necessarily those of the Editor, the Editorial Group, the EMRSN Steering Group or Parkinson's UK.

The next deadline for the March edition is **Monday 31 March**. Please send us a copy of your newsletter and event notices.

Editor: Ian Billcliff (imb248@outlook.com)

Editorial Group: Lionel Paulo, John Telford, Chris Johnson

We look forward to hearing from you!

Visit our page on the Parkinson's UK website:
http://www.parkinsons.org.uk/content/east-midlands-research-support-network