

Medical Writing

Obesity and Type 2 Diabetes

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Themes of upcoming issues of *Medical Writing*

The theme of the March 2013 issue is '**Medical Writing Education**'. The issue is now closed.

The theme of the June 2013 issue is '**Medical Writing around the World**'. The deadline for feature articles is 15th February 2013. Articles are requested on medical writing needs and opportunities in regions not currently well represented or served: Northern Europe (Nordic countries), Southern Europe (Spain, Portugal, and Italy), Central and Eastern Europe, East Asia (Japan, China, etc.), India and Southeast Asia, the Middle East, and Africa.

The tentative theme of the September 2013 issue is '**Health Economics and Market Access**' to coincide with the theme of the May 2013 conference in Manchester. The deadline for feature articles is 19th June 2013.

All correspondence relating to these issues should be addressed to editor@emwa.org.

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The horror and the pity: Obesity and diabetes

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Editorial

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Something less beguiling for a horror-story addict than the emergence of obesity would be hard to imagine. Start by reading the 27 August 2011 issue of the *Lancet*. One article predicts that the obesity rate in the UK will make the tremendous leap from the 25% it is today to 40% by 2030, when its consequences will cost the National Health Service in the UK an extra £2 billion a year. Add to this that more recently researchers reported the body mass index (see illustration of its origin of on page 272), which is used to determine adiposity, underestimates the number of people currently classified as obese by 39%¹ and it's not difficult to succumb to obesophobia (see the Box on page 264). After reading the *Lancet* you might move on to Peretti's² article published in the *Guardian* in June this year. Peretti explains that on average people in the UK are 19 kg heavier than they were in the mid-60s. We are not exercising less but we need to exercise more to counteract our change in diet. The main cause for the increase in obesity, which is also associated with an increased risk of many other disorders most notably diabetes type 2, is that we are consuming large quantities of high-fructose corn syrup. This supplement was surreptitiously introduced into our diet by the food industry in the 1970s. Peretti's article recounts a riveting and plausible theory of the political-industrial conspiracy that allowed this disaster to happen.

Next you should read this issue of *Medical Writing*. You could be forgiven though for asking why, however fascinating and horrific, a medical writing journal should devote an entire issue to obesity and type 2 diabetes. Unlike clinical trials related to cancer and paediatrics featured in recent issues of *MEW*, diabetes trials do not have sensitive and unique features that affect the preparation of reports on the procedures and results. But, with the incidence of obesity and diabetes set to soar, medical writers are bound to find themselves writing more and more about obesity and diabetes in the future. Accumulating knowledge of the diseases we write about is important. The GATE principles, which define the interaction between medical writers and authors, require that writers

have sufficient expertise in the topic or field.³ Nevertheless, an editor at *Gastroenterology* has stated that in her experience professional medical writers often have only limited knowledge of the diseases they write about.⁴

Another reason for focussing on diabetes is personal. I started my career in medical writing as managing editor of *Diabetologia* and before I pass on the editorship of *Medical Writing* to Phillip Leventhal, I am keen to highlight obesity and diabetes type 2 as diseases we should all be vitally concerned about.

The pity is that both diseases are largely preventable through diet and physical exercise. An obvious question, then, is why we don't act in our own best interests: eat sensibly and exercise sufficiently to avoid the dire consequences that we are fully aware of. It's a question that Diana Raffelsbauer asks in her article on obesity. Together with Melanie Price she also examines the evolution and causes of obesity: the contribution made by genetic factors, a lack of physical exercise, and 'toxic food environment'. Did you know that while the price of the flagship healthy food, fruit and vegetables, increased by 118% in the USA between 1985 and 2000, the cost of carbonated soft drinks, which are particularly fattening, only went up by 20% over the same period? Or were you aware that, according to the latest research, genetic susceptibility to obesity is modifiable? In these two comprehensive articles you will also learn about the frustrating and recurring cycle of new anti-obesity drugs entering the market only to be withdrawn when their side effects emerge. As a result, the invasive bariatric surgical procedure, which is reviewed in Diana's article, is still the most successful treatment for moderate and severe obesity.

Laura Cascales gives us an overview of the anti-diabetic drugs traditionally prescribed to control diabetes 2. Unfortunately, they have their problems too, not least that (with the exception of metformin) they cause patients to do the last thing they want to do: gain weight. New incretin-based therapies are now being developed that seem to circumvent the undesirable effects associated with current therapies

and they could herald a new era in the treatment of diabetes, subject to the outcome of long-term safety studies.

Somewhat surprisingly, despite increasing emphasis on the need for exercise, the extent of its importance for maintaining good health appears to have been underestimated and the underlying mechanisms are still not clearly understood. In a fascinating article in this issue, Donal Gorman explains how exercise affects the body and discusses why its study is set to make a major contribution to our knowledge of chronic diseases in the coming decade. Association studies have already linked over 30 chronic diseases to inactivity. A phase has now been reached in physical inactivity research when its relationship to the causes of chronic diseases needs to be investigated in clinical trials. Enter the medical writer!

Two articles in this issue focus on important new initiatives that are currently at the consultation stage and have been undertaken to tackle the obesity and diabetes pandemic. Peter Schwarz's article outlines the Global Diabetes Survey initiative in reply to the United Nations' proclamation that national plans for prevention and control of diabetes need to be developed and monitored to ensure a high quality of diabetes management throughout the world. You as a medical writer are invited to contribute as a stakeholder in this initiative.

EURADIA, the Alliance for European Diabetes Research, is running a consultation process on the development of the European Platform for Clinical Research in Diabetes (EPCRD). The European Union has established the European Council for Health Research, which is roughly modelled on the National Institutes of Health in the USA, for the better co-ordination of medical research in the European Union and to provide common resources and an overarching science policy. EURADIA is concerned that the forthcoming European Commission Research Framework Programme (Horizon 2020) will allocate sufficient funding to diabetes research in Europe. Sarah Hills works with EURADIA and explains in her article in this issue how Europe is falling behind the USA in clinical research. She stresses that without greater investment in diabetes research towards improved prevention and more effective care, total costs will become prohibitive as a result of increasing numbers of people with diabetes and ageing of the European population. EURADIA has proposed the EPCRD model to co-ordinate European clinical research in diabetes

and offer common resources, training, and standardised protocols.

Phobias

It is fairly easy to guess that obesophobia means a fear of becoming fat. Pyrexiphobia, however, is not a fear of Pyrex dishes but of fever. You can find an amazing list of phobias at <http://www.indianchild.com/phobias.htm> Don't miss the footnote at the end warning you that after seeing the list you may have developed a fear of words, which is called logophobia.

I felt that it was very important to publish an explanation of copyright in this issue because with the changeover of publishers questions have arisen from the membership, which call for an independent and clear account of reasons, rights, and obligations surrounding copyright. I am therefore pleased to include Pippa Smart's informative article on the topic in this issue.

These are the last articles I have commissioned and reviewed for *Medical Writing*. They are excellent articles and I am pleased to be ending my 8 years as editor of the journal on this high note. I would like to take this opportunity to thank all the authors who have freely given their time to writing articles for the medical writing community over these past years. I am also very grateful to all those people who have been closely associated with the journal as columnists, section editors, and copy editors. Without their essential contributions EMWA would not have the thriving journal it has today. Finally, thanks to Phillip Leventhal for taking over the editorship and my best wishes to him in carrying the journal forward into a bright future.

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Passing the torch

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This issue is the first where I will be serving as Editor-in-Chief of *Medical Writing* (MEW). Elise Langdon-Neuner, Editor-in-Chief since 2004, will be stepping down. This is yet another step in the evolution of the journal.

For those of you unfamiliar with its history, MEW started life in 1993 as a newsletter produced by European chapter of the American Medical Writers Association, EMWA's predecessor. The newsletter was originally named *The AMWA Journal – Europe* and eventually became *The EMWA Newsletter* with the creation of EMWA in 1995. The newsletter continued to grow with EMWA, becoming *The Write Stuff* (TWS) in 1998 thanks to the creative energy and hard work of Barry Drees, its first Editor-in-Chief. Barry carried TWS through its adolescence, learning on the job about how to format and run a professional journal. (I can imagine that was a lot of fun but probably also pretty stressful.)

In a 2008 article summarizing the first 10 years of TWS, Barry says 'it was with immense satisfaction that I was able to pass the position on to Elise Langdon-Neuner in 2004 and to watch the incredible job she has done continuing to develop and expand TWS'.¹ Just looking at the covers of TWS in the online archive, you can see what he means: essentially alone, and through an enormous amount of volunteered time, Elise elevated the content and format of TWS, bringing the journal into a sort of early adulthood, giving the journal a professional look and feel. Over the last several years, Elise single-handedly managed almost all aspects of the journal. This year, she brought the journal into adulthood, with a transformation from TWS, a private journal limited to EMWA, to MEW, a fully professional, international journal.² Despite some growing pains during the transition, thanks to Elise, we are now ready for the next level of development.

During the last couple of years, in addition to growing and maturing the journal, Elise has prepared the child to leave the nest, that is, to pass

the editorship to the next generation. Elise has greatly simplified this by engaging a professional publisher, Maney Publishing, who is now handling production and publicity.

Although I am now officially Editor-in-Chief, Elise will continue until the end of 2012 as Associate Editor and in the future as Emeritus Editor to help ease me into the post. I am pretty sure that nobody (certainly not me) will again be able to dedicate as much time and effort to the journal as Elise did. Indeed, as the journal expands, there is no way that this can remain a one-person job. Accordingly, one of my first steps has been to create 'section editors' who will function semi-autonomously.

In addition, to help MEW expand beyond EMWA and become broader and truly international, I plan on seeking new contributors from both within and outside of EMWA – and not only from Europe. Also, I am seeking out new regular columns and articles on topics outside the traditional base of EMWA, such as medical journalism and writing for lay audiences; medical communication and medical education; writing for nurses; and veterinary medical writing. Finally, I am working with Maney Publishing to continue to streamline production and communication.

As noted by Keith Veitch, the first editor of *The EMWA Newsletter*, and re-emphasized by Barry Drees, 'an association of writers should be capable of producing a world-class journal, since it represents what we do for a living'.¹ Elise and the other editors before me have done a great job putting us in the right direction, and I plan to continue heading towards that goal.

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Message from the President

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Dear Medical Writers

I expect I am not the only one who at this time of year looks at their calendar in disbelief and asks how on earth another 12 months can have disappeared so quickly? The end of the year is always an especially busy time, but it is an appropriate moment to recollect, to review and assess, and of course to look forward to the future.

This has been a year of important milestones for EMWA. Firstly, the organisation celebrated its 20th Anniversary and over the last 20 years has grown from a small group of enthusiasts to a fully fledged professional association with over 1000 members worldwide. Paralleling the growth of the association, the number and variety of workshops offered by EMWA has expanded from a single 3-hour session at the second conference held in Eindhoven, Netherlands in 1993, to the current impressive total of 60 different workshops offered at the spring conference in Cyprus in 2012. All of these workshops are run on an entirely voluntary basis and the 'spare' time dedicated by the workshop leaders year after year is a reflection of the commitment and selflessness that represent the spirit of our organisation.

The second milestone this year has been the change in the EMWA journal, which now has a new professional glossy look and a new name – *Medical Writing*. The credit for bringing the journal from its humble beginnings as a members' newsletter to a publication which can easily compare with other professional journals lies largely with two individuals – Barry Drees and Elise Langdon-Neuner. In their role as Editor-in-Chief, first Barry and later Elise committed huge amounts of their time to the publication of the journal and it is only thanks to their incredible efforts that it has evolved to become the *Medical Writing* journal we know today. Immeasurable thanks are due to both of them for their dedication and hard work over the past years. As Phil Leventhal steps up to take on the challenge of following in their footsteps, I know he is grateful that

Elise will remain in the background to support him as Emeritus Editor.

Looking forward to the coming year, the Executive Committee and Head Office are already in the middle of preparations for the next Spring conference on 7–11 May in Manchester. The format will be slightly different from that of previous conferences as, in addition to the usual workshop programme, there will be a 1-day symposium with invited guest speakers giving lectures based around the conference theme, Health Economics, Outcomes Research and Market Access.' We hope that this will increase the educational value of the conference and appeal to medical writers and other professionals who are looking for further education and information on this very current and relevant health topic.

Next year there will also be several positions up for election on the Executive Committee – Public Relations Officer, Honorary Secretary, Treasurer, Education Officer, and Vice President. So if you are interested in participating more actively in the organisation and would like to stand as a candidate for one of these positions, please get in touch with either myself president@emwa.org, Head Office info@emwa.org, or another member of the Executive Committee. If you want to find out what the position entails then you can look up to the relevant job description on the EMWA website under 'Contact Us' and 'Executive Committee.' We look forward to hearing from many volunteers!

Finally, as the festive season approaches and the array of tempting goodies in the shops lure us to overindulge ourselves, the theme of the December issue of the journal 'Obesity and Type 2 Diabetes' may help us to moderate our appetites and certainly provides interesting insights into this important health issue. So on that note I would like to wish everyone a very happy, and hopefully also, healthy Christmas and a successful, productive, and prosperous New Year!

December 2012

36th EMWA Conference in Manchester (May 2013)

We are pleased to announce that the 36th EMWA Conference will be held at the Manchester Central Convention Complex, Manchester, England between 7 and 11 May 2013. The theme of the conference is *Health Economics and Market Access*, which will also be the subject of EMWA's very first *1-day symposium* with invited speakers and expert panel members as part of the conference. As usual, EMWA's unparalleled selection of credit and non-credit workshops will be on offer, and there will be plenty of time for networking during breaks and at the evening social events. We look forward to welcoming you in Manchester!

Further information on the conference will be available on the EMWA website (emwa.org) in January 2013.

Obesity: When weight becomes unbearable

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Abstract

Obesity is associated with many chronic diseases. The dramatic rise in its prevalence worldwide has become a major health concern. This article discusses some of the controversies on its causes, consequences, and standard treatments, with a focus on anti-obesity drugs and bariatric surgery.

Keywords: Obesity, Overweight, Diet, Anti-obesity drug, Bariatric surgery, Gastric bypass

What is obesity?

Obesity is defined by the World Health Organization as a body mass index (BMI) of $\geq 30 \text{ kg/m}^2$, whereas overweight lies in the transition zone between this and the normal weight limit (BMI < 25).¹ The prevalence of obesity has risen dramatically over the last two decades, and this has serious consequences for our healthcare and financial systems. Overweight and obesity are associated with a variety of chronic diseases, including musculoskeletal problems, type 2 diabetes mellitus, cardiovascular diseases, and cancer. Weight reduction lowers not only their incidence but also the severity of symptoms or associated health risks once they become chronic. Therefore, keeping body weight within the normal range ($18.5 < \text{BMI} < 25$) is a good strategy to prevent life-threatening diseases.

Causes

Apart from specific endocrine and neurological disorders, the cause of overweight is simple: more calorie intake than calorie expenditure. This leaves us three options: (1) to eat fewer calories; (2) to expend more calories through physical activity; or (3) both. If we are becoming obese, then the logics is that: (1) we are eating more or foods and drinks with more calories; (2) we are physically less active; or (3) both. If the problem is clear, then the solution should also be, at least in theory. All we need to do is: (1) to eat less or less caloric foods;

(2) to become physically more active; or (3) both. But if the principle is so simple, why is obesity becoming a global epidemic with huge impacts on our healthcare systems and economies? Don't we know what to do to avoid becoming obese? If we know, why doesn't it work? These questions aren't simple at all, and there are many possible answers: (1) we don't know exactly what we are eating (think about industrialised, energy-dense foods, and drinks); (2) we know what we are eating and eat it anyway; (3) we can't change our sedentary lifestyle, either because we don't have time to, don't want to, or both; (4) we don't care about our body weight, either because we are not aware of the health risks associated with obesity or because we don't care about our health. But obesity is a burden in most aspects of life: a health-related, quality of life-related, social, professional, and economical burden. It also affects psychological dimensions such as self-acceptance, self-esteem, mood, social interactions, and sexuality.

It seems though that overweight is not simply the result of a mathematical equation. There are various genetic, epigenetic, endocrine, neurological, and environmental factors that contribute to its genesis (see article by M. Price in this issue). And there are also many psychological, social, cultural, and economical aspects in gaining, maintaining, or losing weight.

A few social and economic aspects

Centuries ago, obesity was a synonym of wealth, and this perception is still valid in some cultures where undernourishment is present. But worldwide, today's reality shows the opposite: overweight and obesity are highly prevalent across all social classes. They have recently been linked to lower educational status and professional achievement, and consequently lower incomes, a situation that reminds us of Aristotle's 'the chicken or the egg causality dilemma.' A small, but interesting

experimental study published recently showed that obese people are discriminated by human resource professionals in Germany when they apply for a job.² Obese people (and especially women) were more often disqualified from being hired and less often nominated for a supervisory position, while non-ethnic normal-weight individuals were favoured. This study suggests that weight-related stigmatisation is not only a public health problem, but also a social and economical one.

Obesity is the leader of a wealthy market that incessantly demands new products (weight-management programmes, diets, drugs, and surgical approaches), not least fostered by the ideal of beauty. Everyone who takes a brief look at the newspaper stand is astonished at the number of different diet recipes in most women's magazines, which often also provide details on which diets were effective in whom among prominent people. The food industry has long identified the huge market potential of diet products, as anyone can see in every supermarket. Of course, it is important to look at the calorie content of the food we buy. But aren't 'diet' potato chips a kind of legitimisation to consume an unhealthy product or even the consent to eat double the amount with 50% less calories each?

Prevention and conventional treatment

The most successful programmes for long-term weight control involve combinations of diet, physical activity, and behaviour modification. Physical activity is recommended as a component of weight management for prevention of weight gain, for weight loss, and for prevention of weight regain after weight loss. The American College of Sports Medicine published a Position Stand that recommended moderate-intensity physical activity between 150 and 250 minutes/week to prevent weight gain, whereas greater amounts of physical activity of at least 250 minutes/week are necessary for clinically significant weight loss as well as weight maintenance after weight loss.³ In observational studies, individuals who successfully maintained large weight loss during at least a year typically engaged in about 7 hours/week of moderate- to vigorous-intensity exercise. Physical activity seems to be more important than a normal weight to reduce the risk of type 2 diabetes and cardiovascular diseases.

It is beyond the scope of this article to give an overview on the different types of diets, as not only their scientific evidence and efficacy vary, but also their use and popularity according to personal

preferences and vogue. For instance, according to the *Medical News Today*,⁴ the eight most popular diets in 2009 were: the Atkins diet (low-carbohydrate (carb), high-protein, high-fat), the Zone diet (balance of 40% carbohydrates, 30% fats, and 30% proteins in every meal), the Vegetarian diet, the Vegan diet, the Weight Watchers diet (diet based on a points system, exercise, and a support network), the South Beach diet (low-glycaemic index (GI) products, whole grains, specific fruits and vegetables, olive oil, and lean protein sources), the Raw Food diet (foods and drinks which are not processed, are completely plant-based and ideally organic), and the Mediterranean diet (plant foods, fruits, beans, nuts, cereals, seeds, olive oil, cheese and yogurts, moderate amounts of fish and poultry, up to four eggs per week, small amounts of red meat, and low/moderate amounts of wine). Two years later, the British Dietetic Association's⁵ list of the 10 most popular commercial diets was: the Dukan diet (low-carb, high-protein, restricted vegetables and fat), the Atkins diet, the Cambridge diet (meal replacement products), the South Beach diet, the Slimming World diet (low-fat foods and support network), the Slim-Fast diet (meal replacement products), the LighterLife diet (meal replacement products and weekly counselling), the Weight Watchers diet, the Rosemary Conley diet (low-fat, low-GI diet, and regular exercise), and the Jenny Craig diet (one-to-one support, a meal delivery service, and tailored exercise plans).

Most of us with overweight would be happy to get rid of a couple of excess kilograms. Willingness and self-discipline come spontaneously to my mind. It is however difficult to lose weight because it requires a whole change in behavioural patterns to which we are usually resistant. Otherwise, we wouldn't be overweight. It is also extremely frustrating to regain weight as soon as we return to normal eating habits after following a fad diet. To lose weight and maintain weight loss over the long term, it is necessary to modify one's diet and engage in regular physical activity. So maintaining the new weight needs sustainability. Not only this, depending on the extent of overweight, some people may need additional medical treatment, particularly when their physical and/or psychological health is seriously compromised (for instance, when they are unable to engage in physical activity). These are patients who are at increased medical risk because of their weight. They may be considered for a pharmacological therapy or a bariatric surgery. But before this, they should ideally have tried conventional measures to lose weight through dieting and physical activity without success.

Anti-obesity drugs

Anti-obesity drugs act through one of three distinct mechanisms: suppression of appetite, increase of the body's metabolism (i.e. caloric expenditure), or impairment of digestion and absorption of nutrients (e.g. fat). Since amphetamines were banned from diet pills in 1979, a number of anti-obesity drugs have been launched and withdrawn from the market due to safety concerns. These include aminorex (withdrawn in 1972 due to pulmonary hypertension), fenfluramine, and dexfenfluramine (withdrawn in 1997 due to case reports of heart valve disease and pulmonary hypertension), rimonabant (withdrawn in 2008 due to increased risks of depression and suicidal ideation), and sibutramine (withdrawn in 2010 due to increased risk of heart attacks and strokes).

Weight-loss medications currently approved by the Food and Drug Administration (FDA) for short-term use (≤ 12 weeks) include the appetite suppressants phentermine, diethylpropion, phendimetrazine, and the newcomer lorcaserin. People taking these drugs usually lose 5 kg more than they would normally lose without medication, with the maximum effect seen within the first 6 months. Currently, the only anti-obesity medicine approved by the FDA for long-term use (< 1 year) is the lipase inhibitor orlistat (Xenical[®]).⁶ It was approved by the FDA in 1999 and is available over the counter in the USA since 2007. Drugs used off-label to combat overweight include some anti-depressants (e.g. bupropion), the anti-convulsants topiramate and zonisamide, and anti-diabetic medicines metformin, exenatide, and pramlintide. These substances are currently being studied in more detail regarding their benefit against obesity.

As seen by the number of drugs withdrawn from the market, anti-obesity medicines may cause serious and life-threatening side effects, and these side effects are often inherent to their mechanism of action. Therefore, caution is recommended for prescription and use of any anti-obesity drug. For instance, it is obvious that stimulants increase heart rate and blood pressure, and cause restlessness and insomnia. One of the main issues with anti-obesity drugs is the fact that we do not fully understand the neurological basis of appetite and how to modulate it, as there are so many hormones and neurotransmitters involved in eating, generating, and processing satiety signals. Likewise, there are many parameters controlling storage, bioavailability, and expenditure of energy to keep an adequate balance between anabolism and catabolism. Anti-obesity drugs are not a practical long-term solution

for people who are chronically overweight or obese. In general, they are approved only for people with a BMI ≥ 30 , or a BMI ≥ 27 with an obesity-related condition, such as hypertension, type 2 diabetes, or dyslipidaemia.⁶

What is bariatric surgery?

A different option for extremely obese people is bariatric (weight loss) surgery. Weight loss is achieved by reducing the size of the stomach with an implanted, adjustable medical device (gastric banding), or through removal of a portion of the stomach (sleeve gastrectomy or biliopancreatic diversion with duodenal switch), or by resecting and re-routing the small intestine to a small stomach pouch (gastric bypass surgery).⁷ The gastric bypass is considered the 'gold standard' in the USA (140 000 procedures performed in 2005), and its most common form is the Roux-en-Y gastric bypass.

Bariatric surgery is scientifically proven to be more successful in reducing weight in moderate and severe obesity than conventional treatments.⁸ It allows loss of huge amounts of weight (up to 50 kg) by reducing the size of the stomach as well as the levels of ghrelin (the hormone that causes hunger) it produces.⁹ The smaller stomach constrains the daily amount of food taken and requires a thorough change of dietary patterns after surgery, as overeating causes nausea and vomiting. Also, the resulting reduction in the absorption surface of the small intestine may lead to the need of nutritional supplementation with minerals and vitamins, often for life.¹⁰

Bariatric surgery results in resolution of major obesity-related co-morbidities, including type 2 diabetes, hypertension, dyslipidaemia, metabolic syndrome, non-alcoholic fatty liver disease, nephropathy, left ventricular hypertrophy, and obstructive sleep apnoea in the majority of morbidly obese patients.¹¹ Through these effects, bariatric surgery appears to reduce cardiovascular morbidity and mortality.

The US National Institutes of Health recommend bariatric surgery for obese people with a BMI ≥ 40 , or for people with BMI ≥ 35 , and serious co-morbidities.¹² In line with this, the American Diabetes Association recommends bariatric surgeries only for adults with BMI > 35 and type 2 diabetes, especially if the diabetes or its associated co-morbidities are difficult to control with lifestyle and pharmacological therapy.¹³ In its 2012 Standards of Medical Care in Diabetes, the Association states that 'gastric reduction surgery (either gastric

banding or procedures that involve bypassing, transposing, or resecting sections of the small intestine) can be an effective weight loss treatment for severe obesity, and US national guidelines support its consideration for people with type 2 diabetes who have BMI > 35.' Furthermore, they note that 'bariatric surgery has been shown to lead to near or complete normalization of glycaemia in 55–95% of diabetes patients, depending on the surgical procedure.'

A meta-analysis of studies of bariatric surgery involving 3188 patients with diabetes reported that 78% had remission of diabetes (normalisation of blood glucose levels in the absence of medications), and that the remission rates were sustained in studies with follow-up exceeding 2 years.¹⁴ Weight loss and diabetes remission rates were higher with procedures that bypass portions of the small intestine than with those that only constrict the stomach. This and other studies suggest that intestinal bypass procedures may have glycaemic effects that are independent of their effects on body weight, perhaps involving the incretin axis (hormones that increase insulin release). In a study published in 2010 involving 110 patients with type 2 diabetes and a mean BMI of 47, Roux-en-Y gastric bypass resulted in a mean loss of excess weight of 63% at 1 year and 84% at 2 years.¹⁵ Diabetic medication was discontinued in 68% of the patients and reduced in a further 14%. Two recently published single-centre studies comparing bariatric surgeries with conventional medical therapy in obese diabetic patients reported greater weight loss, better glycaemic control, and reduced use of medicines to treat co-morbid conditions in significantly more patients in the surgical groups,^{16,17} and these effects were independent of pre-operative BMI and post-operative weight loss.¹⁷

Rates of morbidity and mortality directly related to bariatric surgeries have been reduced considerably in recent years.¹³ In a systematic review and meta-analysis published in 2007, total mortality at ≤30 days was 0.28% and total mortality at >30 days to 2 years was 0.35%.¹⁸ Mortality rates were dependent on the type of procedure (open × laparoscopic, restrictive × malabsorptive type), the surgeon's experience, as well as on the pre-operative health status of patients. The most common post-operative complications of bariatric surgery include gastric dumping syndrome (bloating and diarrhoea after eating), anastomotic and staple line leaks, hernia, infections, pulmonary events, and haemorrhage.¹⁹ Morbidity rates are lower after laparoscopic procedures, which is the largest proportion of bariatric operations. Longer-term concerns include

vitamin and mineral deficiencies, hypocalcaemia, osteopaenia, osteoporosis, hyperparathyroidism, development of gallstones, renal diseases, and rarely, Wernicke's encephalopathy and hypoglycaemia resulting from insulin hypersecretion.^{7,19}

In line with the higher incidence of obesity and reflecting improvements in the surgical technique, the number of bariatric surgeries performed worldwide is rising exponentially. Recent scientific evidence suggests that bariatric surgery could be appropriate for those with a BMI = 35–40 with no co-morbidities, or a BMI = 30–35 with significant co-morbidities,^{19–21} further expanding the number of patients who could be considered for the procedure. Bariatric surgery appears to be a clinically effective and cost-effective intervention for moderately to severely obese people compared with non-surgical interventions.^{22,23} However, studies so far available on whether bariatric surgery reduces long-term morbidity and mortality by curing or preventing the onset of chronic diseases are limited and in general difficult to conduct due to several confounders. More efforts are required to monitor the long-term safety and efficacy (particularly in regard to quality of life and overall life expectancy) of bariatric surgery, for instance, by setting up large patients registries and following patients for a longer time.

Conclusions

Diet, physical activity, and behavioural changes remain the first-line treatment for overweight and obesity, but these measures may not be sufficient to promote a clinically significant and sustained weight loss in morbidly obese people. Current anti-obesity drugs also have limited efficacy. If all else fails, bariatric surgery may be considered for people with BMI ≥ 35 at increased health risk. Bariatric surgery results in greater weight loss than conventional treatment, remission of obesity-related diseases such as diabetes and hypertension, and significant improvements in quality of life.^{8,11} However, the pros and cons of each procedure must be carefully weighed up individually in view of short- and long-term benefits and risks.

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The body mass index (BMI) was proposed by Adolphe Quetelet as long ago as 1835. He based it on average measurements from a population of Scottish soldiers.

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Genetics and environmental factors in obesity and diabetes: Complex problems, complex solutions

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Abstract

Over the centuries people have become taller, heavier, and stronger. One of the major reasons for this is the increasing supply of calories in our diets. In earlier times, weight gain was extremely beneficial for health, well-being, and lifespan, but in 2012 we are at a point where weight gain has gone too far and is now detrimental. We are facing an overeating epidemic and the adverse health effects of obesity. This article discusses some of the causes of obesity and the factors affecting it.

Keywords: Obesity, Environmental factors, Genetic factors, Obesity-related diseases, Type 2 diabetes

A global problem

Obesity is a plague of modern society. Only 50 years ago, there were no statistics on obesity, but according to the World Health Organization (WHO), worldwide, obesity has more than doubled since 1980.¹ The harsh reality today is that half a billion people, representing 12% of the world's population, are considered obese.² And the prevalence keeps rising, fuelled by a lifestyle of bad diet and inactivity. But are these the only players?

The WHO defines obesity as an abnormal or excessive accumulation of fat that may impair health. The measure most frequently used in epidemiological studies to classify body condition is the body mass index (BMI), which is calculated as the weight in kilograms divided by the square of the height in metres. The WHO considers a BMI ≥ 30 kg/m² as obese.¹ Despite the popularity of the BMI, a major limitation is that it does not distinguish fat mass from lean mass.³

At first, obesity was a problem of high-income countries and only seen in adults, but more recently,

it has spread to middle- and low-income countries and to children and adolescents.³ Childhood obesity leads to an increased risk of obesity later in life.^{4,5} In 2010, 44.2% of men and 48.3% of women were obese in the USA. Obesity is also present in Latin America. For example, in Chile, 39.1% of women are considered obese. This is also a particular problem in the Caribbean, with, for example, 52.7% of women obese in Trinidad and Tobago. In Europe, the situation is also alarming: 26.3% of women were obese in the UK in 2010. Figures are also creeping up in Southeast Asia and the Middle East, where the population has historically been thin. In China, 1% of men were overweight in 2002 but 4.1% were obese in 2010. However, an incredible 45% of men in China are considered overweight (BMI ≥ 25 kg/m²). Africa is dealing with the double burden of undernutrition and obesity, the latter being now a particular problem in large African towns. In South Africa, for instance, 36.8% of women are obese. The worst affected region in the world is the Pacific Islands. For example, in Nauru, 84.6% of men were overweight in 2010.⁶

Hand in hand with obesity come obesity-related disorders. In fact, we now live in a world where overweight and obesity are linked to more deaths worldwide than underweight.¹

Is obesity self-inflicted?

How do we become obese? Obesity is a gradual process resulting from an energy imbalance in which the energy taken in (calories from food and drinks) exceeds the energy going out (calories used up by physiological activities and physical activity). The end result is that excess energy is stored as body fat deposition: too much fat is a major risk factor for many diseases. This seemingly

simple energy imbalance is, however, driven by a complex mixture of genetic, environmental, psychosocial, and cultural factors.⁷

The prevalence of obesity started to increase drastically from the mid-1980s.³ Since our genomes have remained mainly unchanged for generations, it seems that lifestyle changes in the past few decades have had a major role in the rise of obesity prevalence. Globally, there has been an enormous increase in the consumption of unhealthy foods that are high in sugar, fats, and salt and low in nutrients and vitamins. This includes a global increase in the intake of sugary drinks, which are considered to make up a large part of the increased calorie intake leading to obesity.⁸ Portion sizes have also increased and so has the consumption of processed and convenience foods, which contain high levels of sugar and fat. Another global change is that lifestyles have become more inactive and jobs more sedentary. People more often use transport instead of walking, they spend long hours in front of computers and TVs for work and leisure, and they spend little energy because everything is nearby and on-hand.

Although obesity is considered self-inflicted, social and economic changes associated with development also influence our lifestyle choices. For example, many towns have been built without sidewalks or not providing enough space for children to play in an active way. Also, healthy foods may be inaccessible or too expensive in many cases.⁹ Obesity is closely related to socio-economic status, with a higher prevalence among poorer and less-educated individuals.³ In addition, school cafeterias may not offer healthy menus, and parents may not teach healthy lifestyles.

To make matters worse, the agricultural and food industries have often selected food options for their customers based on profit rather than health. In America, between 1985 and 2000, prices for fruits and vegetables increased 118% but only 35% for fats, 46% for sugars, and 20% for carbonated soft drinks.¹⁰

Chemicals in our environment may also add to the problem, as certain chemicals have been shown to cause metabolic changes.^{11,12} Endocrine-disrupting chemicals from packing and food processing, such as bisphenol A (BPA), can be detected in foods and in the urine and serum of most humans. Experimental studies in animals have revealed an association between low-dose foetal exposure to BPA and obesity at puberty.¹³ This was also observed in an American study in humans.¹⁴ Early antibiotic use in infants (<6 months of age) has also recently been linked to obesity.¹⁵ Other possible

factors include lack of sleep and certain medications and illnesses.¹⁶ For example, BMI is inversely correlated with sleep duration, and obesity is associated with some psychological problems and with smoking cessation.

Is it all in our genes?

Despite this 'obesogenic' environment, some individuals remain thin and do not go on to become overweight and obese, whereas some of the overweight can't manage to lose weight. This suggests that in a population exposed to the same environment, there is inter-individual variation in obesity susceptibility, suggesting that biological mechanisms or genes influence obesity. Obesity is known to run in families, and family and twin studies have shown that BMI is 40–60% heritable.¹⁷ Abdominal obesity, measured by waist circumference (WC) or waist-to-hip ratio (WH ratio) and considered a more reliable predictor of risk for metabolic complications of obesity, is 45–60% heritable.¹⁸

In the mid-1990s, several studies examined the role of genes suspected to be involved in obesity on the basis of their expression in cases of extreme or early-onset obesity and evidence from transgenic animal models. Mutant mice accumulating five times the normal amount of body fat were found to lack the single *ob* gene. This gene is active in fat cells and produces a protein that reaches the brain via the bloodstream to signal satiety. This protein was named leptin from the Greek word *leptos*, which means thin. Studies of *db* mice, a second model of obesity, were found to lack the gene for the leptin receptor and therefore could not receive the satiety message.^{19,20} Several conditions of childhood obesity have been linked to mutations in these genes.^{21,22} Mutations in the melanocortin receptor gene were also found to cause severe early-onset obesity.²³ Furthermore, obesity is a common phenotype shared by several different syndromes, including Prader-Willi syndrome, Bardet-Biedl syndrome, a sub-phenotype of Fragile X syndrome, and WAGR syndrome.²⁴ However, these single gene defects are rare and the total of all the cases does not get close to the average 33% prevalence of obesity worldwide.²³

Towards the end of the 1990s, genome-wide linkage studies revealed approximately 300 chromosomal loci associated with obesity, but a single causal gene or variant was not found. Genome-wide association studies (GWAS) started in 2005 have been more successful.^{25,26} Two million genetic variants were tested for association in extremely large, non-related samples. GWAS screening

for obesity-related traits (BMI, WC, WH ratio, body fat percentage, and extreme-early onset obesity) led to the discovery of 52 robust loci.^{24,26} For BMI, 32 loci reaching genome-wide significance have been identified for white European-type adults. Of the 32 loci identified by Speliotes *et al.*,²⁷ eight are strongly linked to an adjacent common missense SNP (single-nucleotide polymorphism), and 15 contain genes that may be linked biologically to obesity. Despite the enormous success of GWAS, the established loci explain only a fraction of the heritability (approximately 2–4%). At present, knowing an individual's genotype at all eight loci does not provide a clinically viable test for obesity risk.²⁶ In fact, two traditional predictors of obesity – childhood obesity and parental obesity – appear to be the only reliable predictors of obesity risk in adult life.²⁸

However, GWAS has been extremely useful in identifying genes in the susceptibility loci, thus allowing new hypotheses about the biology of common obesity.²⁹ *FTO* was the first obesity-associated gene to be described and is expressed in hypothalamic feeding regions.^{29,30} It may affect food intake, as carriers of the risk allele have been shown to prefer energy-dense and more palatable foods.²⁹ Some of the genes (e.g. *MCR4*, *POMC*, and *BDNF*) were previously known to be involved in monogenic obesity.²⁷ Another gene, *SH2B1*, causes obesity when knocked out in mice and appears to be involved in leptin signalling.³¹ Interestingly, many of these genes are highly expressed in the brain, particularly in the hypothalamus, suggesting a central role for the brain in the predisposition to obesity.²⁴ One of the most recent variants maps within the *GIPR* gene, which encodes an incretin receptor. This receptor is thought to play a role in nutrient sensing and insulin secretion in the periphery, suggesting that variations in insulin secretion may be involved in the development of obesity.²⁷ Speliotes estimates that 250 common variant loci for human obesity remain to be discovered and that many more loci with smaller effects will probably be identified.²⁷ These loci might be found in more extensive searches and by broadening searches to include children, adolescents, and adults of non-European descent.

Both environment and genetic disposition appear to participate in the development of obesity. A classical example of such a gene-environment interaction comes from the Pima Indians. Sixty-nine per cent of the Indians who live in the 'obesogenic' environment of Arizona are obese, while only about 30% of white Americans in the same environment are obese. In the 'restrictive' environment of

Mexico, however, only 13% become obese, suggesting that something in the Pima Indian's genetic makeup predisposes them to obesity.¹²

Is there evidence that lifestyle factors can interact with the robust genetic loci described above? A number of studies report that physical activity attenuates the association between the *FTO* locus and obesity traits.³² Such gene-physical activity interactions provide an important health message to the public: the genetic susceptibility to obesity may be modifiable.¹² Recent research points towards the possibility of changing gene function without changing genomic sequences. Perinatal metabolic programming appears to influence early-life obesity via epigenetic effects.¹² Another influence on genetics is assertive mating for obesity, which is estimated to have increased the prevalence for obesity in the population by about 5%.¹²

To put the current obesity epidemic into an evolutionary context, we need to consider our ancestors. O'Dea³³ believes that humans are still adapted to the ancestral hunter-gatherer diet and lifestyle. Hunter-gatherers used different strategies to survive, including gorging in times when food was abundant, preferring energy-rich foods, and minimising energy expenditure by only performing necessary physical activity. Our 'obesogenic' society is exactly what the hunter-gatherers would need to survive: an abundance of energy-dense food, easily available, with minimal effort, and at low cost! However, without the periods of 'famine' in between, the sad consequence of our biological adaptation to hunger is the global epidemic of obesity and related habits.

What are the consequences of being obese?

Health consequences

Research has shown that, as body weight increases to the level defined as obese, several pathologies appear. On a social level, the increased mass of adipose tissue leads to disabilities, including effects on the quality of life such as shame, depression, disability, physical discomfort, sexual problems, and social isolation. Excess fat may also lead to sleep apnoea, due to increased abdominal pressure on the diaphragm and reduced lung volume, as well as stress on the joints leading to osteoarthritis. The risk of a second set of diseases is increased by the metabolic changes associated with obesity, as pathogenic products are released from the larger and more numerous fat cells.³⁴ This includes an increased risk of type 2 diabetes,

coronary heart disease, hypertension, cancers (endometrial, breast, and colon), metabolic syndrome (a combination of high blood sugar, high blood pressure, high triglycerides, and high cholesterol), dyslipidemia (e.g. high total cholesterol or triglycerides), stroke, non-alcoholic fatty liver disease, gallbladder disease, and gynaecological problems (abnormal menses, infertility). Obesity may also accelerate cognitive decline and increase deficits in academic achievement.^{35,36} Risks of all of these problems are greater not only with obesity but also with overweight.

Most of the diseases associated with obesity are deadly. On average, obesity reduces life expectancy by 6–7 years, and it has become one of the leading preventable causes of death in the world.³⁷ The Centers for Disease Control and Prevention estimate that, in the United States, an excess of 112–365 000 deaths per year can be attributed to obesity.³⁸ The majority (>80%) of these deaths occur among people with a BMI greater than 30 kg/m².

Financial consequences

The medical costs of obesity are shocking. In the USA in 2005, costs totalled about \$190.2 billion or 20.6% of all medical expenses.³⁸ In the UK, the National Health Service spends about £5.1 billion per year on obesity-associated medical costs, and with people living longer, the costs are expected to keep rising.³⁹

Type 2 diabetes: one of the strongest risks of obesity

In 2011, 366 million people worldwide had diabetes (90% were type 2) and 4.6 million people died from the consequences of high blood sugar. Eighty per cent of those deaths occurred in low- and middle-income countries, where the burden of diabetes has increased at a dramatic rate.⁴⁰ Today, the WHO estimates that 1 in 10 adults suffer from diabetes – a startling global prevalence of 10%.⁴¹

Type 2 diabetes is caused by the body's ineffective use of insulin bought on by excess body weight and not enough physical exercise. The risk of type 2 diabetes increases with the level and the duration of being overweight and with the amount of visceral fat, which is the fat deposited around the abdominal organs. A study of the association between diabetes and BMI showed that at a BMI of 35 kg/m², the relative risk of type 2 diabetes increased 40%. However, even thin people are at risk of diabetes if they lead a sedentary or unhealthy lifestyle, such as low physical activity, irregular eating, eating a poor diet, and emotional stress, because they increase the

build-up of 'invisible' visceral fat.³⁴ Type 2 diabetes usually appears in people over 40 years of age, but in South Asian and African-Caribbean people, it often appears after the age of 25. Also, children, some as young as 7 years of age, are more often being diagnosed with the condition.⁴²

In the USA, diabetes cost \$465 billion in health-care expenses in 2000, a staggering 11% of the total healthcare expenditure. The WHO estimates that between 2006 and 2015, China will lose \$551 billion in income due to heart disease, stroke, and diabetes. The situation is grave in the poorest countries, where people with diabetes and their families bear most of the cost of the medical care.⁴⁰

Conclusions

Obesity reduces physical fitness, increases the risk for chronic diseases and disability, and significantly shortens lifespan. This has repercussions throughout communities, including reduced performance in school and at work, poor health and well-being, and massive increases in health costs.

As discussed above, becoming obese and suffering chronic diseases is not just a matter of overeating and being lazy but results from multiple and complex interactions between our genes and environments. Obesity cannot easily be fixed with fad diets or trendy exercise programmes. Indeed, the Healthy People 2010 Program set a 10-year national objective to improve obesity and nutrition in the USA.⁴³ The target to reduce obesity to 15% in this period completely failed and, despite national efforts, obesity actually increased from 1988 to 2008 by 47.8%. Similarly, healthful eating patterns remained well below their 2010 targets. It seems that neither individuals nor societies alone are able to change the increasing obesity incidence. Therefore, healthcare professionals, policy makers, and politicians need to make the types of changes that will lead to a supportive environment with affordable and accessible healthy food choices and physical activity. Some options could be to subvent healthy foods, to charge higher taxes for sugary or fatty foods, to promote physical activity by supporting local sport clubs, and to reward initiatives aimed at preventing overweight and engaging in healthy lifestyles. Why don't governments use a bonus point system to give financial compensation for those active in obesity and diabetes prevention? The savings in healthcare costs would be substantial, and commercial weight management programmes have shown that this strategy works.

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Clinical pharmacology series

Obesity

A growing problem...

Obesity is now a global phenomenon. It has reached epidemic proportions; almost a billion adults are overweight and one-third of these individuals can be classified as clinically obese (BMI ≥ 30 kg/m²). In the USA the age-adjusted prevalence of obesity is 33.8% overall. Obesity can result in pathophysiological changes in regional blood flow, lean mass and an increase in fat mass. A recent review discussed the implications of obesity for drug therapy¹. Alterations to pharmacokinetics (PK) and pharmacodynamics (PD) and any consequent requirement for dose adjustment were investigated. The authors summarised that obesity had greatest effect on the absorption of drugs given parenterally. Drug distribution was likely to be affected by changes in the volume of distribution, tissue perfusion and plasma protein binding. Both CYP and Phase II-mediated drug metabolism were altered by obesity. For drugs that were renally excreted, increased weight led to difficulties in calculating glomerular filtration rate (GFR). Additionally, GFR plus tubular secretion and reabsorption were altered in obesity. Overall, it was concluded that the changes in drug disposition in obese populations are highly variable and dependent on several factors, including drug characteristics, degree of obesity and patient-specific organ function.

A review of drug product labels and approval packages found limited information on dosing guidance in obese patients. It was recommended that the evaluation of PK and PD in obese populations become incorporated into the general drug development process.

In children

An increase in obesity has also been recorded in the paediatric population. A US report found the prevalence of obesity to be 17% in the age group 2–19 years. The consequences of obesity in this population for the disposition of drugs is less well studied compared with adults. Nevertheless, studies are starting to appear in the literature. A recent investigation examined whether

obese and healthy-weight children vary with respect to drug metabolising enzyme activity². The activity of the oxidative enzymes CYP1A2 and xanthine oxidase (XO) were studied along with the conjugative enzyme activity of N-acetyltransferase 2 (NAT2). No difference was observed in CYP1A2 activity. For both XO and NAT2 enzyme activity was elevated in the obese population. These findings mirrored results found in adults. It was concluded that further studies were required in the obese paediatric population, in order to determine the clinical consequences on dosage for drugs that are metabolised by these enzymes.

Drug Development

Clinical pharmacology aims to ensure that the right dose is given to the right patient at the right time. To do this an understanding is required of the inherent variability present in any patient population and the effect that it may have on drug response. Clearly obesity is a factor that may alter the PK/PD response and the consequent therapeutic dose. Given its prevalence obesity provides a further challenge for the drug innovator!

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New treatments for type 2 diabetes

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Abstract

Type 2 diabetes (T2D) has become a burden for society, and the incidence of the disease continues to increase. A range of therapies is available to control glycaemia in T2D patients; however, these drugs have undesired side-effects and there is a need to develop improved treatments. Extensive research in diabetes has led to a better understanding of the disease and therefore to the design of new therapies. Incretin-based therapies are of special interest because they have numerous advantages over traditional treatments, for example, they do not produce hypoglycaemia and they induce weight loss, reduce appetite, provide β -cell protection, and reduce the risk of cardiovascular disease. There are two different incretin therapy approaches: glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors. In this article, the incretin-based therapies available on the market are described and compared with the traditional therapies to control diabetes. Finally, preventive steps are pointed out as an option to control diabetes, which has become a pandemic of the twenty-first century.

Keywords: Diabetes, Diabetes treatments, Incretin, GLP-1, DPP-4, Obesity

Introduction

Diabetes is a chronic disease in which either insulin production is impaired or insulin is used inefficiently by the body. Insulin is a hormone that is released by pancreatic β -cells in response to an increase in plasma glucose levels after food intake. In patients with type 1 diabetes (T1D) the body cannot produce insulin and the patients are insulin-dependent, meaning that they need to inject insulin to survive. In patients with type 2 diabetes (T2D) the body does not release enough insulin or it becomes insensitive to insulin, also known as insulin resistance. T2D accounts for 90%

of the cases of diabetes and will be the focus of this article.¹

Currently, 346 million people have diabetes in the world, a number that continues to increase.² This increase has been attributed to changes in diet and lifestyle. Generally, a sedentary lifestyle and the consumption of more fats and sugars are the causes of T2D. The complications associated with diabetes are numerous, including cardiovascular disease, stroke, and microvascular complications that can lead to blindness and renal failure. Therefore, diabetic patients have a reduced quality-of-life and life expectancy, not to mention enormous health costs. In the United States alone, diabetes costs were 174 billion US dollars in 2007.³ Therefore, there is an urgent need to prevent and control this disease, which has become a burden for society.

Conventional treatments for diabetes: the long history of insulin and more

Insulin has been used to control glycaemia in diabetic patients since 1922.⁴ Long-lasting formulations of insulin and many other treatments have been developed. Conventional treatments to control hyperglycaemia in diabetes include insulin, insulin analogues, insulin secretagogues, and insulin sensitisers.

- *Insulin analogues* with improved properties compared with basal insulin have been developed.⁵ The long-acting *insulin glargine* is injected only once daily. It is marketed as Luntus[®] by Sanofi-Aventis. Likewise, Novo Nordisk has the long-acting *insulin degludec* in clinical trials, and so far, it appears to have similar properties as *insulin glargine*.
- *Insulin secretagogues* are drugs that stimulate pancreatic β -cells to secrete insulin. They include sulfonylureas and meglitinides.⁶

- *Insulin sensitisers* decrease insulin resistance by improving insulin sensitivity. Biguanides (*metformin*) and thiazolidinediones fall into this classification.⁷ Nowadays, *metformin* is the first choice of medication to treat T2D, together with changes in diet and increased physical activity.

These conventional medicines have been useful in controlling diabetes, but many problems remain. In particular, conventional medicines have associated side-effects, such as hypoglycaemia, which is particularly an issue with sulfonylureas and insulin therapy. The conventional medicines, especially sulfonylureas, can also cause β -cell destruction. In addition, with the exception of *metformin*, most antidiabetic drugs cause weight gain, which is an added problem for the many diabetic patients that are obese. Thus, drugs with fewer side-effects and that do not cause weight gain – or even better, produce weight loss – are desired.

Research in the last decade has provided a better understanding of diabetes and led to the development of new treatments. Drugs based on incretin hormones are especially interesting and are discussed below.

Incretin hormones: a gut feeling

Incretin hormones are released from the gut within minutes of eating a meal, causing what is known as the ‘incretin effect.’ Incretin hormones stimulate the secretion of insulin by pancreatic β -cells and are therefore insulinotropic hormones. In healthy individuals, the incretin effect is responsible for 50–70% of the insulin secreted after a meal.⁸

Two incretin hormones have been identified: glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP and GLP-1 are released from the K-cells and L-cells of the intestine, respectively. Studies with exogenous incretins have shown that GIP does not stimulate insulin secretion in T2D patients.⁹ Conversely, GLP-1 stimulated insulin secretion in diabetic patients and is therefore the focus of drug development efforts.

When secreted, GLP-1 lowers plasma glucose to normal levels, inhibits glucagon secretion, delays gastric emptying, decreases appetite, and increases pancreatic β -cells proliferation.¹⁰ GLP-1 is only secreted when food is ingested and not when glucose is injected intravenously (the so-called incretin effect). The intracellular effect of GLP-1 is mediated by the GLP-1 receptor (GLP-1R), a member of the G-coupled protein receptor (GPCR) family that is expressed in many tissues.

GLP-1 has a very short half-life (approximately 1.5 minutes). The active form of GLP-1_{7–36}, which is referred to as native GLP-1, is cleaved by the enzyme dipeptidyl peptidase-4 (DPP-4), generating the inactive peptide GLP-1_{9–36}.⁸ Therefore, the administration of exogenous GLP-1 as a therapy is not feasible because it is rapidly inactivated. Two approaches based on incretin hormones are being developed for the treatment of diabetes: (1) GLP-1 analogues that activate GLP-1R and are resistant to DPP-4 and (2) inhibitors of DPP-4, which act by increasing the half-life of endogenous GLP-1.

GLP-1R agonists: emulating GLP-1

The rapid degradation of GLP-1 by DPP-4 has encouraged scientists to develop GLP-1 analogues that are resistant to degradation. Two GLP-1R agonists are already on the market.¹¹ *Exenatide* was approved in the USA in 2005 and is marketed under the name Byetta[®] (Amylin Pharmaceuticals). *Liraglutide* was approved in Europe in 2009 and is distributed by Novo Nordisk as Victoza[®].

Exenatide is a synthetic version of exendin-4, a naturally occurring 39-amino acid peptide originally isolated from the saliva of the Gila monster lizard (*Heloderma suspectum*), and it shares 53% amino acid sequence identity with native GLP-1.¹² By contrast, *liraglutide* shares 97% amino acid sequence identity with GLP-1; it has one amino acid substitution and an added glutamate-linked fatty acid side chain that promotes albumin binding.¹³

Exenatide is administered intravenously twice daily. A once-weekly formulation has recently been approved and is marketed under the name Bydureon[®]. *Liraglutide* is administered once daily intravenously, a disadvantage compared with *metformin*, which can be taken orally. However, *exenatide* and *liraglutide* have many advantages over *metformin*. Since they are glucose-dependent, they do not induce hypoglycaemia, a common problem with the conventional diabetes drugs. In addition, they promote weight loss, may improve pancreatic β -cell function, and may reduce the risk of cardiovascular diseases.¹⁴ This last point is of paramount importance since cardiovascular complications are the most common cause of morbidity and mortality amongst T2D patients.¹⁵

Altogether, GLP-1R agonists appear to be promising molecules for the control of T2D. Clinical trials to date have reported few side-effects, mostly nausea and stomach discomfort that tends to resolve after a few weeks of treatment. However, the long-term safety of GLP-1R agonists remains to be determined. Tumours have been observed in

the thyroid tissue of rodents treated with *liraglutide*,¹⁶ although whether *liraglutide* causes thyroid tumours in humans is not yet known. Thus, the long-term consequences of sustained GLP-1R activation in the human thyroid require further investigation. For this reason, GLP-1R agonists are currently only recommended as second- or third-line therapies in T2D, only when *metformin* and other traditional therapies are not effective in controlling the disease.

Apart from *exenatide* and *liraglutide*, there is a long list of new molecules in the development pipeline.^{11,17} Among others, *lixisenatide* (Sanofi-Aventis), *albiglutide* (GlaxoSmithKline), *semaqlutide* (Novo Nordisk), *LY2189265* (Eli Lilly & Co.), and *CJC-1134-PC* (ConjuChem) are currently in clinical development. Clinical trials of *tasoglutide* (Roche) have been suspended due to safety concerns.

DPP-4 inhibitors: another pro-incretin alternative

A second approach based on incretins to control glycaemia in diabetic patients is to block DPP-4 with inhibitors. DPP-4 is the enzyme that degrades endogenous GLP-1 and is widely distributed throughout the body.¹⁸ Molecules that inhibit DPP-4 increase endogenous GLP-1 concentrations two- to three-fold, depending on the inhibitor.

The DPP-4 inhibitor *sitagliptin* (Januvia[®] by Merck & Co.) was approved by the FDA in 2006, followed by *saxagliptin* (Onglyza[®], Bristol-Myers Squibb), *vildagliptin* (Galvus[®], Novartis), *linagliptin* (Tradjenta[®], Boehringer Ingelheim and Eli Lilly & Co.), and *alogliptin* (Nesina[®], Takeda, currently only approved in Japan).

DPP-4 inhibitors are administered orally, an advantage over GLP-1R agonists that have to be injected intravenously. Like GLP-1R agonists, DPP-4 inhibitors do not produce hypoglycaemia and might preserve β -cell function. However, DPP-4 inhibitors do not affect gastric emptying or decrease appetite and therefore do not promote weight loss. Nevertheless, they are considered weight neutral, which is an improvement over other treatments. Clinical trials suggest that DPP-4 inhibitors reduce cardiovascular risk, although more studies are needed to clarify the relationship between the use of DPP-4 inhibitors and cardiovascular protection.¹⁹ Overall, DPP-4 inhibitors appear to be less efficient than GLP-1R agonists in lowering plasma glucose levels.²⁰

The various DPP-4 inhibitors available on the market differ in their potency, metabolism, and excretion route.^{21,22} Understanding the

pharmacological properties of the different drugs is necessary for choosing the appropriate therapy for each patient. The most common side-effects of DPP-4 inhibitors are an increased risk of infections (nasopharyngitis, upper respiratory tract infections, and urinary tract infections) and headaches. However, the consequences of long-term DPP-4 inhibition in T2D patients are unknown. Therefore, like GLP-1R agonists, they are a second- or third-line option used when conventional therapies fail to control hyperglycaemia.

Prevention of diabetes: the clue to stopping the disease?

Although genetic factors influence the risk of developing diabetes, obesity is well established as the main cause of T2D.²³ In 2008, 1.4 billion people were overweight (body mass index ≥ 25), of which 500 million were obese (body mass index ≥ 30).²⁴ Worldwide, obesity has more than doubled since 1980, which explains the outbreak of diabetes in the last decades. The increase in obesity is attributed to the modern sedentary lifestyle, with diets rich in fats and sugars. Obesity can be easily prevented by introducing changes in diet and lifestyle. Targeting obesity in order to control diabetes is therefore a logical strategy.

Obesity is a key risk factor for T2D since it is the main cause of insulin resistance.²⁵ An individual can be obese and be insulin resistant but will not necessarily develop diabetes. Pancreatic β -cells compensate for insulin resistance by producing more insulin. T2D occurs when β -cells are damaged and are unable to compensate for insulin resistance, which leads to hyperglycaemia. The release of increased amounts of free fatty acids from adipose tissue in obese individuals is a crucial factor linking obesity, insulin resistance, and impaired β -cell function. Furthermore, obesity-induced tissue inflammation leads to the release of pro-inflammatory cytokines and the activation of protein kinases known to participate in the development of insulin resistance.²⁶

The Finnish Diabetes Prevention Study suggested that the incidence of diabetes can be reduced by lifestyle intervention. The study found that relative risk of contracting T2D was reduced by 43% by controlling body weight, increasing physical activity, and reducing the amount of fat consumed. Another study conducted by the Diabetes Prevention Program Research Group found that in individuals at high risk for diabetes, lifestyle changes and treatment with *metformin* reduced the incidence of diabetes, although lifestyle changes were far more

effective than *metformin* alone (58 and 31% reduction in incidence, respectively).²⁷ Interestingly, dietary changes produce spectacular improvements in the insulin sensitivity of T2D patients, challenging the paradigm that T2D is a chronic disease.²⁸

Conclusion

T2D has become a global disease of pandemic proportions. New treatments to treat diabetes have emerged and many more are in the pipeline. The increasing number of therapies has led various clinical bodies such as the American Diabetes Association, the European Association for the Study of Diabetes and the National Institute for Health and Clinical Excellence in the UK, to develop guidelines to help physicians choose the best treatment for patients. Currently, *metformin* is the first option to control the disease due to its glucose-lowering effects, absence of weight gain, relatively few side-effects, and relatively low cost. However, additional treatments are needed when *metformin* fails to control glycaemia.

Incretin-based therapies offer an exciting new approach and have valuable advantages over conventional therapies. GLP-1R agonists and DPP-4 inhibitors control glycaemia in a glucose-dependent manner and therefore do not cause hypoglycaemia. In addition, they seem to increase pancreatic β -cells proliferation and to reduce cardiovascular risk. The ability of GLP-1R agonists to promote weight loss is especially interesting since most T2D patients suffer from obesity. Incretin-based therapies are currently second- or third-line therapies in T2D, mainly because long-term safety studies of these drugs have not yet been completed. However, the promising results obtained so far in clinical trials suggest that they will largely replace conventional therapies.

Diabetes is a serious disease that in many cases can be prevented. Obesity appears to be the main cause of T2D, and often simple changes to lifestyle can prevent this condition from ever developing. Educational campaigns to inform the public about the associated risks of obesity are extremely important. Motivating people to make changes in lifestyle by modifying eating habits and increasing physical activity would save health care systems and society in general a great deal of money and would increase the quality of life of people suffering from obesity and diabetes.

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Is exercise physiology a real science?

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Abstract

Exercise physiology has not always been held with the same regard as other scientific disciplines. Despite the often held view that it is confined to the study of sport, exercise physiology has contributed to some of the most important scientific advances, particularly in understanding metabolic function. The physiological stress of exercise provides a unique model to understand the regulation of energy expenditure, gene expression, and glucose utilisation. In the future, it will also be required to better understand how physical inactivity contributes to the development of chronic diseases. Therefore, the contribution of exercise physiology to the advancement of scientific knowledge should not be underestimated.

Keywords: Exercise physiology, Physical activity, Metabolism, Gene expression, Mitochondrial function, Glucose transport

Exercise physiology is a sub-discipline that focuses on the functional responses and adaptations associated with physical activity or inactivity. As physiology is often best studied under extreme conditions, exercise provides an excellent experimental model to answer important scientific questions.

One of the best and earliest examples of this approach was the research of Professor A.V. Hill for which he received the Nobel Prize in 1922. In order to better understand heat production in muscle, Professor Hill measured total work performed during exercise and the energy expended to perform the work. He was able to establish that the human body was not very efficient at converting stored energy into mechanical energy and instead produced heat which had to be dissipated from the body. This work is still relevant today and has formed the basis for much of the exercise physiology textbooks.

Introduction

The role of exercise in the realm of scientific endeavour is not always met with acceptance. In some eyes, exercise is merely the participation in sporting activities that require little in the way of experimentation, objectivity, or the creation of knowledge. For others, exercise is recognised as something we should do but a relatively insignificant contributor to our understanding of chronic diseases. However, for a small but dedicated group of physiologists, exercise is one of the most fascinating and powerful experimental models.

Physiology is an integrated science that advances our understanding of the function of the human body. It provides the basis for broad areas covered by medicine and disease prevention as well as more specific disciplines such as molecular biology, immunology, and environmental biology.

Glucose transport and diabetes

In more recent years, the dramatic increase in the prevalence of type 2 diabetes has focused research to better understand glucose uptake. Under normal circumstances, ingested glucose stimulates the release of insulin. When insulin binds to receptors, mainly on muscle, liver, and fat cells, a series of intracellular events occur that result in glucose transport proteins being translocated into the cell surface and facilitate glucose uptake. Individuals who increase body weight or develop type 2 diabetes become resistant to the action of insulin. As a result, a smaller number of glucose transport proteins are inserted into the cell membrane and compensatory actions, such as increased insulin production, are initiated to maintain glucose homeostasis.¹ A concerted effort to characterise the insulin signalling cascade has produced thousands

of papers in the past two decades but the pathway is not yet fully characterised.

While insulin is the most important hormone for lowering blood glucose, it has been known for some time that exercise also lowers blood glucose levels in healthy individuals and those with abnormal glucose tolerance.¹ When the insulin signalling cascade was studied during exercise, it was found not to be activated² though glucose transporters were translocated.³ Therefore, exercise facilitates glucose disposal independently of the actions of insulin, providing a scientific basis for exercise in the treatment of type 2 diabetes, but also a model to identify novel pharmacological targets. This work has found that stress responsive cascades (AMPK and p38 MAPK) and calcium signalling, resulting from the contractile process, are the main pathways that promote glucose uptake during exercise.¹ The significance of these pathways and their potential as non-insulin-mediated glucose-lowering targets continue to be explored.

Gene expression and epigenetics

The genomic era brought great promise of gene targets that would explain the basis of human health and disease. The advancement in technology that made these techniques accessible and affordable was of benefit, but also influenced the nature of research questions. A lot of emphasis was placed on determining the effect of individual genes on whole body and tissue-specific responses. As this research is not possible in humans, with the exception of rare monogenetic diseases, there was a shift towards animal and cell-based research. The impact of exercise physiology during this period was blunted but the post-genomic era has greater potential. The proportion of human diseases with genetic causes, even polygenetic, might be smaller than initially anticipated, but the interaction between environmental factors and the epigenome may play a major role.

Epigenetic modification has emerged as a key regulator of gene expression. While the DNA sequence remains unchanged, some of the individual nucleotides that make up the DNA are methylated, altering efficiency of gene transcription. The epigenetic signature is heritable and much of the focus has been on determining if traits of chronic diseases are passed from parent or grandparent to offspring in this manner. However, it has also recently emerged that DNA methylation can be modified by exercise. In healthy but inactive individuals, whole-genome methylation was decreased after an

acute bout of exercise.⁴ It was also reported that hypomethylation of the promoter region of key metabolic genes, and the subsequent expression of mRNA, was dependent on the intensity of the exercise. These changes were evident 3 hours after exercise but were not observed following a period of exercise training, which suggests that exercise acutely regulates the epigenetic profile and gene expression. Further research is required to determine the time course of these changes and whether exercise can modulate the heritability of epigenetic modification.

The argument for exercise-mediated regulation of gene expression is quite strong. The human genome has evolved to support physical activity, and if our ancestors could not hunt and gather effectively, they would not have survived. Consequently, the gene expression profile, in particular the metabolic gene profile, reflects the demand for energy production and the amount of physical activity.⁵ One clear example of this is the number and size of mitochondria, the aerobic powerhouse of cells. Individuals who exercise on a regular basis have a greater number of mitochondria than inactive, obese or type 2 diabetic individuals. Exercise is quite a potent stimulator of metabolic gene expression and can significantly increase the expression of many mitochondrial proteins in 7–14 days, leading to mitochondrial biogenesis in just a few weeks. However, the amount of mitochondria is malleable and a sustained period of inactivity will require a smaller amount of energy production and therefore a reduction in the energy-producing machinery of mitochondria.

At another level, exercise has played an important role in elucidating the regulation of transcription factor complexes. Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1 α) is a transcriptional co-activator that has been proposed as a coordinator of metabolic gene expression. PGC-1 α expression is increased in skeletal muscle by exercise and has been implicated in many of the adaptations associated with exercise, including mitochondrial biogenesis, angiogenesis, muscle fibre composition, and glucose transport.⁶ In fact, the same intracellular proteins activated by exercise to facilitate glucose transport are translocated to the nucleus and mediate PGC-1 α transcription.

A consequence of this work has been the identification of an exercise-activated, PGC-1 α -dependent protein, irisin that is released into circulation.⁷ Irisin is a chemical messenger with endocrine action on adipose tissues, promoting

the conversion of white adipose tissue to the more bioenergetic brown adipose. Over-expressing the gene encoding irisin was shown to improve glucose homeostasis and obesity in high-fat-fed mice. Interestingly, irisin was required for many of the exercise effects on gene expression in adipose tissues. Therefore, exercise is an excellent model for understanding the regulation of gene expression and also identifying chemical messengers called myokines that are released from skeletal muscle and communicate with other tissues and regulate physiological processes in an endocrine fashion.

Physical inactivity and risk of disease

The main focus in exercise physiology has been to understand the responses and adaptations to exercise in healthy individuals and those with chronic diseases. However, a paradigm shift is occurring that will very likely change our view of activity, or more importantly inactivity. It has long been assumed that the positive benefits of regular exercise are simply lost with the cessation of training. This view is being challenged by recent findings that physical inactivity can induce separate physiological processes that actively promote, amongst others, muscle atrophy and insulin resistance.⁸ Physical inactivity has been linked to more than 30 chronic diseases but mainly by association studies. The next phase of experimentation will require more direct evidence of a cause and effect relationship by mechanistic studies and randomised controlled trials.

As previously mentioned, the human genome has evolved to support physical activity and in particular our ability to hunt and gather food for survival.⁵ This required a large amount of energy expenditure until recently. Advances in technology have dramatically decreased the requirement to expend energy for feeding. These changes have also impacted on occupational and recreational energy expenditure while at the same time energy intake has increased due to the consumption of energy dense, industrialised products. The net outcome is a positive energy balance and energy storage leading to an increase in fat mass, ectopic fat accumulation, and the development of risk factors associated with the metabolic syndrome, type 2 diabetes, and cardiovascular diseases. In tackling obesity-related diseases, most emphasis has been placed on dietary modification but the contribution of physical inactivity appears to have been underestimated. It is not feasible to continue recommending calorie restriction as we cannot

consume enough of the vitamins and minerals required to maintain normal function. Instead, we need to increase physical activity and allow for nutrient intake that will match expenditure and contribute to health.

Physical inactivity is most often associated with metabolic diseases, but there is increasing evidence for a role in other chronic conditions. One area that is already attracting attention is the link between inactivity and the age-related decline in cognitive function. Those who are less active or have low fitness levels tend to be at greater risk of incident dementia and Alzheimer’s disease. Population demographics show an increase in the number of older people.⁹ Those who exhibit cognitive impairment require more support, supervision, and clinical management with serious implications for the cost of healthcare systems. It is speculated that the increased risk may be associated with a decrease in blood flow to the brain, atrophy of different parts of the brain, or a reduction in neural plasticity, but the evidence is not robust enough at this time to make conclusive statements. In the next decade, exercise/inactivity physiology has the potential to make a major impact on our understanding of chronic diseases.



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Conclusion

In conclusion, the contribution of exercise physiology to scientific endeavour cannot be underestimated. The physiological stress of exercise provides a unique model to investigate normal body function and advance our understanding of the factors that contribute to the development and progression of chronic diseases. Exercise has been used to answer some of the most basic research questions relating to heat production and the role of muscle as an endocrine organ. It has also been used to help treat patients with chronic diseases and will hopefully continue to contribute to the advancement of scientific knowledge.

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What is the best quality of diabetes care? The Global Diabetes Survey needs your participation

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Abstract

Adequate quality of diabetes care and the best concept for the implementation of national diabetes plans remains controversial. In September 2011, the United Nations Summit for Non-Communicable Diseases agreed that national plans for prevention and control of diabetes must be developed, implemented, and monitored. The Global Diabetes Survey (GDS) is a standardised, annual, global questionnaire that will be used to assess responses of representatives from 19 diabetes-related stakeholder groups. It was designed with the goal of generating an annual report on the quality of national diabetes care and to compare findings from different regions and countries. The findings will be freely available and will be used to inform politicians and stakeholders, with the goal of improving the quality of diabetes care. We encourage the public to participate. If you are interested, please go to www.globaldiabetessurvey.com.

Keywords: Survey, Type 2 diabetes, Quality of care, Diabetes mellitus

Worldwide, the number of people suffering from diabetes mellitus continues to increase.¹ This poses a growing health, social, and economic burden. This increase is mostly driven by type 2 diabetes (T2DM), which is increasingly diagnosed at younger ages and is leading to a rapidly growing group of elderly adults (65+) with diabetes.² The increasing average life expectancy also adds to the number of older people living with diabetes. Management of this group poses unique challenges, and current data indicate that outcomes remain far from optimal.³ Furthermore, to optimise the quality of diabetes care, more information about

healthcare structures and individualised patient management is needed.

To respond in a coordinated fashion to the burden of diabetes, the quality and structures of diabetes care need to be assessed in a standardised way. This information can be used to develop and implement national diabetes plans (NDPs), addressing that addressing the goals, processes, responsibilities, quality of care, availability, and accessibility of diabetes care.⁴

In September 2011, at the United Nations Summit for Non-Communicable Diseases, the Ministers of Health requested international cooperation and international policy decisions on diabetes. The consensus from this meeting was that national plans for the prevention and control of chronic diseases have to be developed and implemented, and that strategies to monitor the implementation progress need to be established. The recommendation called for standardised and annual monitoring of the quality of diabetes care in the member states. As these recommendations suggest, one of the critical factors to tackle the diabetes epidemic is the implementation of NDPs that incorporate not only diabetes care, but also public health aspects, diabetes prevention, rehabilitation, and care for associated non-communicable conditions. Several countries have developed NDPs with varying success.⁵ Successful NDPs are specific to the country, and successful investment has been built on extensive knowledge of the structure, process, and outcome quality of diabetes care, coupled with consensus between all relevant stakeholders about how to implement the NDP.³

The Global Diabetes Survey

The Global Diabetes Survey (GDS) is designed to provide data on the quality of diabetes care in

different countries worldwide, with the aim of comparing and providing a benchmark for the quality of diabetes care.

Objectives of the GDS

1. To annually assess the quality of national diabetes care in each participating country.
2. To identify gaps and barriers in diabetes management in the participating countries and combine inter- and intra-country comparisons of best practice, with the goal of providing targeted evidence to decision-makers for the planning, management, and organisation of NDPs.
3. To annually analyse the changes of the quality in diabetes care by using follow-up GDS data.

Methodology of the GDS

To achieve these objectives, two conditions must be met:

1. A standardised set of questions that adequately represents the quality of diabetes care in different countries must be developed.
2. These questions must be answered by GDS stakeholders representing all relevant areas and focus groups in diabetes care.

Development of the GDS questionnaire

The quality of diabetes care will be assessed using a standardised questionnaire. Appropriate items for the questionnaire will be identified by reviewing existing diabetes guidelines and NDPs. The relevance of the identified items will be weighed to select the questions to be included. The GDS questionnaire will then be translated into different languages and an appropriate online format will be developed. The GDS questionnaire will be a standardised and structured questionnaire that will assess the structure, process, and outcome quality of diabetes care in the participating countries and that can be answered by all different stakeholders. This questionnaire is currently undergoing a Delphi-like optimisation by the registered GDS volunteers (more than 1200 worldwide).

Participants in the GDS – diabetes stakeholders

To achieve representative data from each country, a sufficient number of representative stakeholders from 19 diabetes-related groups will be invited to participate in the survey. These stakeholders' groups include individuals involved in diabetes care and disease management:

- Patients or patient organisations
- General practitioners
- Diabetes specialists
- Diabetes educators
- Diabetes nurses
- Other diabetes professions
- Scientists and scientific organisations
- Diabetes prevention experts
- Politicians and policy makers
- Health insurance and payer representatives
- Participants from industry
- Pharmacists
- Indirectly affected persons
- Other interest groups.

The ultimate goal is to recruit one person in each group per 250 000 patients with diabetes per country. In countries where it is not possible to invite stakeholder groups, the different groups must be represented.

Participants will register and complete the survey online. Our initial experience indicates that this is possible in developing countries. To date, more than 1200 stakeholders from more than 100 countries have already registered in the GDS at www.globaldiabetessurvey.com.

Completion of the GDS

The GDS will be performed annually in September/October, with the goal of data analysis to be completed by World Diabetes Day on November 14.

Analysis of the GDS data

Data collected from the GDS will be analysed centrally at the University of Dresden, Germany. The analysis will examine similarities and dissimilarities, as well as stakeholders' views on national diabetes management. In addition, the prevalence, incidence, and diabetes-related healthcare budget will be compared between each country and will be depicted on a global map describing the quality of national diabetes care. The map will be used to identify target countries with the largest needs, with the goal of increasing the quality of diabetes care and providing guidance for disease management and support for the development of NDPs.

Communication of the GDS results

The results of the project will be made available in the scientific and lay press on World Diabetes Day (November 14) via international organisations. The goal is to invite other partners to make use of the experiences and results of the project, and to help improve diabetes care in their countries. The results will be condensed in a report that will

provide politicians with evidence to help them to prioritise chronic care management for people with diabetes mellitus.

Discussion

Concerted action and commitment is needed to fulfil the recommendations of the United Nations Declaration on Non-Communicable Diseases.^{6,7} The GDS is the first initiative that will provide benchmarks on the quality of diabetes care worldwide, including standardised information about structures, processes, and quality of diabetes care. The strategic methodology will provide holistic and realistic information about diabetes care in each participating country. The more volunteer stakeholders that participate, the more specific the country-based picture can be. Benchmarking diabetes care between different countries will – especially with the annual follow-up and communication of results – provide strong evidence to politicians on the gaps in diabetes care.

Adequate communication of the GDS results should empower national and regional decision-makers to plan, manage, and organise health systems by giving them an evidence base. The results will strengthen the ability to develop targeted diabetes policy that addresses the need for better diabetes care. This will help to develop NDPs for diabetes care. It will also help national and regional decision-makers to better translate knowledge, empirical data, and operational experience into policies and plans that improve the effectiveness, efficiency, and equitability of health systems and services.

This GDS will clarify the status quo of national diabetes care worldwide for the first time, and it

will allow progress towards the United Nations Declaration on NCD to be followed. The success of the GDS depends on the participation of enough volunteers. So we warmly invited you to participate in it, no matter where you live. Your participation will be particularly valuable if you belong to any of the named stakeholder focus groups. If you would like to participate, please go to www.globaldiabetessurvey.com.

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The Global Diabetes Survey team is a team of medical specialists, health care researchers, psychologists, and IT

specialists who feel dedicated to activities to improve the quality of diabetes care worldwide. This includes Doreen Ebermann, Antje Lindner, Gregor Gallein, Ulrike Rothe, Gabriele Müller, Jaqueline Schwarz, Istvan Tibor Nebel, Peter Schwarz, and currently 1889 registered stakeholder volunteers from 127 countries worldwide.

The importance of Health Research in Horizon 2020: Diabetes as a model of a chronic disease and the need for sustainable funding

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Abstract

Diabetes is one of the most common chronic diseases and is estimated to affect more than 32 million European Union (EU) citizens, which is nearly 10% of the total EU population. An additional 32 million EU citizens are not yet diagnosed or have pre-diabetes, and rates of diabetes are expected to further rise as the population ages. Annual costs of diabetes in 2010 were approximately €300 billion, and the European Parliament now considers diabetes an epidemic. Horizon 2020, the upcoming European Commission Research Framework Programme, will dictate how much funding is available for scientific research in Europe. EURADIA, the Alliance for European Diabetes Research, is working to ensure that Horizon 2020 will allocate sufficient funding to health research in light of the increasing economic consequences of chronic diseases such as diabetes.

Keywords: Diabetes, Treatment, Europe, Funding, Horizon 2020

Diabetes in the European Union

Diabetes is one of the most common chronic diseases and is estimated to affect more than 32 million European Union (EU) citizens, nearly 10% of the total EU population.¹ An additional 32 million EU citizens are not yet diagnosed or have pre-diabetes.

Type 1 diabetes still cannot be prevented, and its risk factors remain unclear, whereas the complications of type 2 diabetes are preventable through early diagnosis and lifestyle changes. However, type 2 diabetes is frequently diagnosed too late,

and 50% of all people with diabetes are unaware of their condition.²

Diabetes is responsible for over 10% of healthcare expenditure in most EU member states.³ Average healthcare costs for an EU citizen with diabetes are estimated to be €2100 per year.¹ A recent study of the direct and indirect cost burden of diabetes in five EU countries estimated a total of €188 billion for 2010.⁴ Linear extrapolation suggests an annual cost of approximately €300 billion in 2010 for the EU.

EURADIA and funding for diabetes research in Europe

EURADIA, the Alliance of European Diabetes Research, is a unique alliance of non-governmental organisations and pharmaceutical companies with the mission of improving the lives of people affected by diabetes by promoting diabetes research funding in Europe through advocacy and communication. The DIAMAP project, funded by the European Commission, and managed by EURADIA, has examined spending on diabetes research. According to DIAMAP, a total of €0.5 billion was spent on diabetes research in 2008.⁵

EURADIA is continually communicating the message that without greater investment in diabetes research on improving diabetes prevention and care total costs of caring for people with diabetes will continue to rise as the population ages along with an increase in co-morbid conditions, especially heart disease, stroke, blindness, amputation, and kidney failure.

Health research budget in Horizon 2020

Currently, EURADIA is awaiting results of discussion around the legislation for Horizon 2020, the

European Research Framework Programme, which should be in place by the end of 2013.⁶ Horizon 2020 is a financial instrument that implements the Innovation Union, a Europe 2020 initiative aimed at securing Europe's global competitiveness. Horizon 2020's goal is to create new growth and jobs in Europe, and it runs from 2014 to 2020 with an €80 billion budget. Horizon 2020 contains two pillars – *Excellent Science – Research Infrastructure* and *Societal Challenges – Health, Demographic Change, and Wellbeing* – that address infrastructure and funding of scientific investigation for chronic (non-communicable) diseases such as diabetes. Horizon 2020 was developed with the input of many stakeholders and with the help of position statements from many academic institutions and advocacy groups, including EURADIA. EURADIA continues to work with the European Commission to ensure that diabetes research receives adequate funding, as this condition affects so many people.

The European Commission's Seventh Framework Programme (FP7) provided €55 billion for science and research between 2007 and 2013. Although this was increased to €80 billion in Horizon 2020, the proportional allocation for health research decreased from 12% in FP7 to 10% in Horizon 2020.⁷ The Alliance for Biomedical Research in Europe had led a campaign for increased spending on biomedical research to 20% in Horizon 2020, with the aim of speeding the translation of basic science discoveries to healthcare delivery.⁸

Urgent societal challenges

The European Commission has stated that biomedical and public health research contributing to chronic disease prevention and treatment are among the most important areas of research.⁹ Europe's investment in research must correspond to this policy. Therefore, EURADIA urges that the budget for research in healthcare be allocated to reflect urgent societal challenges, in particular:

- *Chronic diseases* (diabetes, cardiovascular diseases, cancer, chronic respiratory diseases, and mental disorders), which account for approximately 86% of deaths and 77% of the disease burden in the European region.¹⁰
- Changing demographics and the ageing population. The population in Europe is ageing,¹¹ so that diabetes is becoming more common.¹²

In March of 2012, the European Coalition for Diabetes, of which EURADIA is a founding member, drafted *The European Parliament Resolution*

on Addressing the EU Diabetes Epidemic, which calls on the Commission to develop and implement a targeted EU Diabetes Strategy via an EU Council Recommendation on diabetes prevention, diagnosis, management, education, and research.¹³

Structural and societal challenges to maintaining European excellence in science

Health research in Europe is in urgent need of better coordination: common resources and an overall science policy are needed. The Alliance for Biomedical Research in Europe proposed creating a European Council for Health Research to be modelled loosely on the United States National Institutes of Health. The purpose of this agency would be to improve competitiveness and excellence in science in Europe, while offering direct benefits to the health and quality of life of EU citizens. EURADIA strongly supports this plan and has made their position known to the European Parliament.¹⁴

Europe has a history of excellence in clinical research that has been lost in recent years to the USA due in part to a lack of training and professional opportunities. At the same time, European citizens are not offered equal participation in clinical studies and are therefore losing opportunities to improve their health and quality of life. Renewed excellence in this critical area could be addressed by creating disease-focused clinical research infrastructure under the umbrella of the proposed European Council for Health Research. EURADIA proposes that a European Platform for Clinical Research in Diabetes (EPCRD)⁵ coordinate European efforts in this area. This platform would mediate sharing of resources, training, and standardised protocols. EURADIA is currently developing the EPCRD via a consultation process. Documents and a questionnaire are available at www.EURADIA.org.

New longer-term instruments are needed to ensure sustained funding under Horizon 2020. The lack of sustainability in funding in FP7 has reduced the return-on-investment for scientific research. This reflects a broader need for long-term, scientifically based strategic planning and science policy in Europe.

DIAMAP, the first European health research road map for diabetes⁵ was followed by FUTURAGE, a road map for ageing research,¹⁵ and ROAMER, a road map for mental health research in Europe.¹⁶ Under Horizon 2020 this road map approach could be extended to the entire health research space. The experience and knowledge gained from

these road maps would give the newly proposed European Council for Health Research a strong foundation for coordinating the European biomedical research effort⁷ and provide the European Commission with a useful benchmark against which future developments could be measured.

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Sarah Hills trained as a nurse at the Middlesex Hospital and the London Chest Hospital in the UK (1980–1986). She worked for the European Association for the Study of Diabetes (EASD) and managed the editorial office of *Diabetologia* (1987–1997) in Uppsala, Sweden and Pisa, Italy. Sarah became the administrator for the European Group for the Study of Insulin Resistance (EGIR) and in 2001 manager of the multi-centre FP5 RISC (Relationship between Insulin Resistance and Cardiovascular Disease) project coordinated at the University of Pisa. From 2008 to 2010 Sarah was manager of the FP7 DIAMAP (Road Map for Diabetes Research in Europe) project. Sarah has also been active in FEND (Foundation for European Nurses in Diabetes) and was the Editor-in-Chief of the journal *European Diabetes Nursing* from 2004 to 2010. Sarah is currently Executive Director of EURADIA.

EURADIA is a unique alliance of NGOs and pharmaceutical companies with the mission of improving the lives of people affected by diabetes by promoting diabetes research funding in Europe through advocacy and communication.

Is anyone stealing your articles? Exploding copyright myths

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Abstract

Management of intellectual property rights, and copyright in particular, is usually handled by publishers on behalf of authors. However, many authors are worried about assigning copyright to publishers and are unclear about what this implies. This article looks at some of the common misconceptions about copyright and explains the truth behind the myths.

Keywords: Copyright, Plagiarism, Authorship

Introduction

Many people consider copyright to be too boring to read about or to be somebody else's problem. However, copyright not only is a fascinating subject, but it is something that every author should know something about.

The main reason that copyright causes problems is the many misconceptions about it. These lead to incorrect assumptions and accusations. In this article I hope to explode some of the common myths.

The concept of protecting ideas and their expression goes far back into history. In ancient Greece, for example, the theft of ideas was identified as a crime, and plagiarism was punishable. The modern concept of copyright started in China in the eleventh century, and in the Western world with the UK Statute of Anne, which was passed in 1710. Soon after the Statute of Anne, other countries (e.g. France) implemented similar laws to protect intellectual property. However, these legal protections only worked within national boundaries and did not protect works from being illegally copied in other countries. With the development of international trade treaties, copyright also became subject of international cooperation with the Berne Convention, originally signed in 1886. Today, 165 countries subscribe to this Convention, which was last updated in 1979. Signatory countries all respect the copyright of the other signatory

countries and afford them the same level of protection as they do for works published by their own nationals.

This means that you, as an author, have (almost) global protection for your work. The practical outcome of this is that if your article is published in a German journal and that article is made available (digitally or in print) in South Korea, then it is protected within Korea under Korean law. This is good news – especially in the digital environment.

Given this globalisation, who actually enforces copyright? As an individual author, if you discover that someone else has copied your work, what do you do about it? This is where publishers are really useful. Publishers are used to investigating and challenging potential copyright infringement. Not only do most of the major publishers have experience and resources to challenge infringement, but publishing associations also work on behalf of member publishers to address international piracy.

Given this international protection, why are there still myths about copyright? Partially, this is due to different national interpretations of the law, and not every country has exactly the same laws. But mostly it is because authors fear to lose something that they have created, and they worry that they are being taken advantage of by publishers.

Myth: only published items are copyrighted

This is the biggest myth. Many authors think that copyright only starts when you publish your article. However, when you, as authors, write anything, it is instantly protected under your national copyright legislation. You don't have to publish it to have ownership of the copyright. Similarly, if you create an image, take a photograph, draw a graph, or record a video clip, it is also protected under copyright law.

Many authors worry about allowing their article to become public before publication in case someone 'steals' it – but in fact the work is protected

by copyright the moment it is written (or video recorded, etc.).

One anomaly that scientific authors may experience is that your employer may actually own copyright on something you create – if it was created as part of your employment. Universities and large research institutions don't usually enforce this, but large corporations and government agencies usually do, although this varies between countries.

Myth: it's OK to copy so long as I credit the creator

Well, no, it's not OK to copy and simply credit the creator. If a work is protected by copyright then you must usually obtain permission to copy. It is allowable to use small portions of a work (e.g. a quotation, etc.) without permission. This is called 'fair use' or an 'exception to copyright,' but this needs to be done carefully.

One common infringement is copying artwork, for example, graphs and charts. Frequently, the author has been asked for permission, but if copyright or exclusive license has been assigned to the publisher, then the author cannot grant permission, although authors frequently think they can! Another problem is that authors who are unable to obtain permission from the publisher (e.g. they are unable to get a response from the publisher) often adapt the figure (e.g. change a bar chart to a line graph) and think that by saying 'adapted from...' they have given correct attribution and have not infringed copyright. This is actually not correct – an adaptation such as this still contravenes copyright if done without permission.

However, there are many publications that allow reuse of all or parts of a work without permission. To find out if you need permission, you should check the licence that the publication uses (Terms and Conditions). For example, some publications may say that you can reuse the work for a non-commercial reason without permission. Some others may say that you can reuse the work for any purpose without seeking permission. See, for example, the Terms and Conditions of the journal, *PLoS One*, which uses a Creative Commons licence that allows any reuse of the content for any purpose without seeking permission (<http://creativecommons.org/licenses/by/2.5/>). See also the *BMJ* licence, which allows use for non-commercial reasons, again using a Creative Commons licence (<http://creativecommons.org/licenses/by-nc/2.0/>).

There is, however, one big question that can be tricky to answer: What is 'commercial' and what is 'non-commercial?' In many cases, this is obvious –

if you are publishing a book for sale, this is commercial, whereas if you want to include content in materials that you hand out to colleagues for free, this is non-commercial. However there are 'grey areas' in-between, so you need to use your judgement – but play safe!

Myth: if I need to seek permission, I will have to pay

No, again, this is often untrue. If you want to include an item within an article (e.g. a graph or an image), then it is unlikely that the copyright owner will ask you to pay for this use. Most publishers who require you to ask permission do so because they want to know what people are doing with their content. So, for example, if you ask permission to use their work for a totally inappropriate reason, they can say 'no!' If you want to reuse their content for monetary gain (e.g. inclusion in a book that you want to sell), then they will probably ask you for a fee. How much this is will depend on what use you want to put the content.

Many publishers are now including a 'rights permission' link on their website for each article. These provide a 'ready reckoner' of charges for commercial uses. But beware: the way these are set up rarely – if ever – grants free permission. So if you honestly feel that your use is non-commercial, contact the publisher directly.

Myth: I need to keep my copyright to ensure that my name is associated with the work

This is definitely untrue! The Berne Convention includes the moral right of attribution. Although this is not enforced in all countries (e.g. the USA), you can assume that it is usually honoured in the scholarly environment. Where it is not honoured, assigning copyright would make no difference!

In some countries you can waive your moral right to be identified as the author of a work (e.g. the UK), but many European countries (e.g. France) will not allow you to do this. When you enter an agreement with the publisher, your name (and that of your co-authors) is identified and should always be associated with your article. Note that the moral right of attribution also covers the right not to be associated with an article that you did not write.

Myth: blogs and tweets are not covered by copyright

This is partially true. Tweets have been deemed to be too small to be covered by copyright, but blogs,

Wikis, and all other web content are protected just as strongly as any printed work. However, determining who owns the copyright in these cases is often difficult! For example, if a journal's online article includes comments from the public, then copyright in the comments may remain with the public authors or may be assigned to the publisher of the website or journal, depending on whether the publisher has included any licence agreement in the comment submission form. Copyright for a blog is usually owned by the blog site owner (e.g. *Nature* owns the copyright for all their blogs), but it may be owned by the individuals who write the blog entries, which is more often the case for less formal blog sites.

Myth: by assigning copyright you lose ownership of your work

Before answering this question, 'ownership' needs to be defined. To most authors, it means the right to reuse your work elsewhere. Whether you can do this depends on the agreement that you sign with the publisher – it is not really dictated by whether you sign over copyright to the publisher or not. Some publishers who require copyright allow authors reuse their works freely, whereas some publishers that ask only for a licence to publish may actually include conditions that allow the authors to do very little with their work after publication.

Most (good) publishers will allow you to retain the rights to reuse your work for non-commercial reasons such as training – and to do so without asking permission from them. Also you will almost certainly be able to produce derivative works (e.g. a book chapter) based on the same content without permission. *Copyright only protects the expression of an idea, and not the idea itself.* Therefore, if you have undertaken some research and write it up as a research article, you will not be infringing on the copyright if you subsequently re-write the research into, for example, a book chapter, or a presentation. However, you must read the contract that you sign with your publisher! Also, it is always good practice to cite your earlier works on which your later works are based. Not only does this confer greater credibility on your current work, but it may help to increase citations and raise awareness of your earlier works.

Publishers are often unwilling to allow you to republish your final work (i.e. the PDF of your final article) in an open repository, but many are willing to allow you to post pre-prints. A pre-print is any version of your article up to, and including, the accepted article but does not include the final

edited and formatted article. You may be required to post such pre-prints, if there is an institutional or grant-funding mandate.

Note that publishers who only ask you to assign them a licence to publish may require an exclusive licence. This means that you are not allowed to republish your work for commercial or non-commercial reasons. Although you retain ownership of your copyright in this case, you still can't make free use of your article. Again, the same principle applies: be sure to read and understand the contract that you have signed.

Myth: copyright infringement and plagiarism are the same

This is a common fallacy, and the difference is frequently misunderstood. Copyright infringement is copying the expression of an idea without permission (with or without attribution). Plagiarism is not attributing the author and pretending that the work is your own. For example, copying an article completely with the author's name but without permission is copyright infringement, whereas copying the article or a portion of the article and replacing the author's name with your own is both copyright infringement and plagiarism. Taking the ideas in the article and using them (unattributed) to write your own article is plagiarism.

In the academic and research world, plagiarism is extremely serious. For example, Hungarian President Pal Schmitt is currently under pressure to stand down after being accused of plagiarising parts of his doctoral thesis. His plagiarism has led critics to question the integrity of his office.

In the legal environment, suing for copyright infringement is often easier than suing for plagiarism because the laws are usually more robust. Also, plagiarising without copying some of the expression used by the original author is quite difficult, so copyright infringement usually occurs in most cases of plagiarism.

Interestingly, most plagiarism-checking software (e.g. TurnItIn and CrossCheck) looks for word similarity. Word similarity may indicate copyright infringement but does not necessarily indicate plagiarism. Not only can the software not check for concepts and ideas, but it can easily miss some plagiarised content. Therefore, these are more accurately called copyright-checking tools.

Myth: the lead author owns copyright

This is not true; all contributing authors share joint copyright ownership in a jointly-authored article. However, if one person created all the figures, then

they would own sole copyright for them. At least in theory, this means that every author should sign the copyright assignment form. In reality, common practice is to only ask the lead or corresponding author to sign the form, but this is legally dubious.

Myth: by submitting the author has implicitly granted the publisher copyright

This is commonly thought to be the case but it is certainly incorrect! Just because the guide for authors says that by submitting to the journal the authors assign copyright to the journal, does not make it so. This assumption is not legally watertight, at least not in all jurisdictions that I know of.

In exactly the same way as websites require you to tick the 'agree to the terms and conditions' box, within publishing, the authors (or the rights owner if this is not the author) must assert copyright assignment or grant a licence to the publisher for the article to be published. This is usually done either as part of the online submission system, or "offline" by signing and returning an assignment form.

Myth: if I cannot assign copyright, I cannot publish with you

Most quality journals will allow authors to sign a licence to publish agreement with them in cases where the author cannot assign copyright. This may happen, for example, if the author works for

a large organisation that owns copyright in all work generated by the organisation and is unwilling to assign it to anyone else. For example, employees of the World Health Organization (WHO) do not own copyright in articles that they create as part of their work. Instead, copyright is retained by the WHO. Therefore, when the author submits the article for publication, the WHO, as owners of the copyright, would have to sign the permissions form and would not assign copyright but only grant a licence to publish the article, reserving the copyright within the WHO.

Conclusion

Copyright protects the creator of a work by identifying them as the creator and protecting their commercial and moral interests. When you sub-contract the work of publishing to a publisher (in return for disseminating your research, increasing your academic/research credibility, and possibly enhancing your job prospects) they can help in protecting your work from being pirated or falsely attributed to another person. However, in return for this, they will often require the freedom to use your work (for the purposes which you agreed in your agreement with them) and may require copyright assignment. Despite this, journals are beginning to ask for an exclusive licence to publish instead of copyright assignment. This makes little difference to the business of the publisher or to the rights of the author but often makes authors feel better.

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Paragraphing (Part 1 of 2)

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Abstract

The purpose of paragraphing is to make text understandable and easy to read, and to help you tell your story effectively. Paragraphing is difficult because the purpose of the documents we produce and their readership are diverse. To make matters worse, little guidance is given in school and during higher education. Paragraphing is not governed by standard rules; some conventions apply but often are – or have to be – ignored in scientific and medical texts. This is the first of two articles on paragraphing and deals with basic issues that face medical writers and editors. The second article will look at developing paragraphs from ideas when you plan a document.

Keywords: Paragraphing, Rules, Topic sentence, Scientific writing, Text flow, Linking words

Paragraphing is not easy. Most of us had little guidance on it in school and higher education, and guidance in books and on the Internet usually doesn't provide much more help than 'not-too-long-not-too-short-and-only-one-idea-per-paragraph'. This guidance also doesn't usually cover the 'special needs' that we often find in the type of documents written by medical writers. Most regulatory documents, for example, are highly structured and leave little room for the type of paragraphing required in a scientific paper. Likewise, in medical communications documentation you often deliberately ignore conventions that you observe elsewhere.

Paragraphing is simply how you split up your text into manageable and logical chunks. How you do it is determined by the type of document you are writing and your audience. As with any other aspect of writing, your target is the reader – reviewer, patient, physician – and your approach to writing must make them want to read on and not give up on your text. Their expectations with regard to paragraphing will also be different if they are reading a scientific paper, Clinical Overview, package leaflet, Periodic Safety Update

Report, or informational booklet on diabetes handed out after diagnosis.

Medical writers and editors are often required to work on a huge range of documents of different styles for different audiences. These documents require different levels of language, precision, and paragraphing. The major split in our field is between regulatory and non-regulatory documentation. But even within a single document, some sections can be paragraphed in the classic manner, while this can be very difficult or inappropriate in other sections.

Paragraphs are a type of macropunctuation

If you ask when a comma is appropriate, most people will say 'when you need a pause in a sentence or when a new clause starts'. Ask the same about when to start a new paragraph, and they will say 'when you need to give the reader a rest or start a new idea'. This means that paragraphing has a similar function to punctuation, but it is 'macropunctuation': punctuation sends out messages to the reader to create meaning by splitting up the words in a sentence, while paragraphing groups sentences with logical breaks to ease reading and help understanding.

Paragraphs should be immediately visible

Separate paragraphs on a page should be immediately visible. In regulatory documentation, such as clinical study protocols and reports, this can be achieved by very simple devices, usually by inserting an empty line between paragraphs or by indenting the first line of a paragraph by about 2 cm, with or without an empty line in between. The devices used must be consistent throughout the document. In regulatory documentation, patient information materials and scientific articles, content always takes precedence over visual aspects.

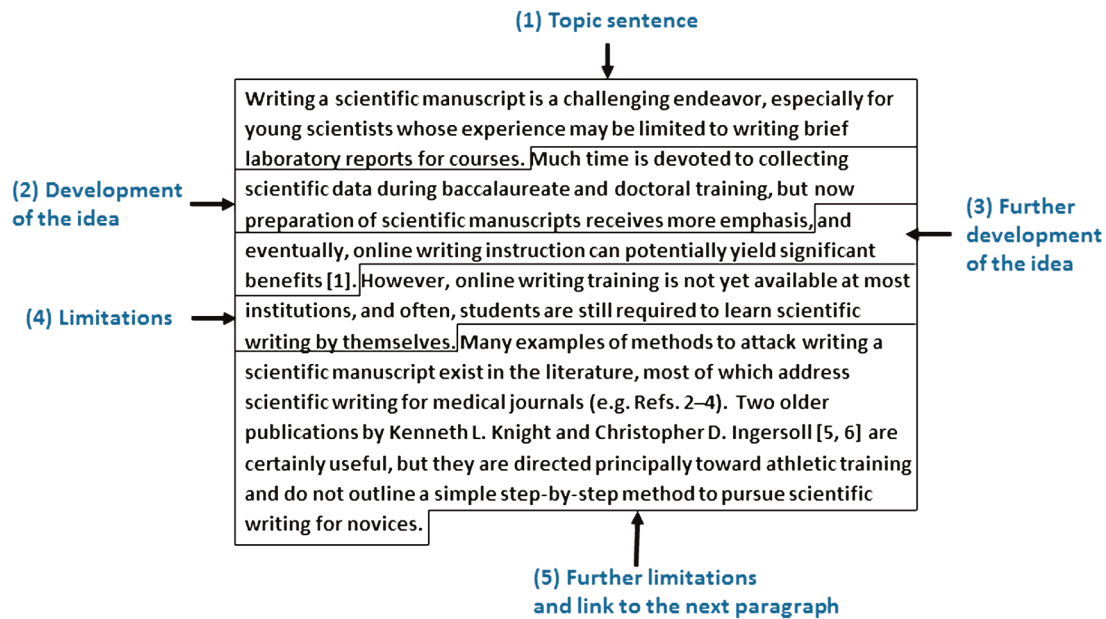


Figure 1: Structure of a typical paragraph.

The approach in marketing documents or on websites is different. Much more striking devices can be used to indicate paragraphs, such as enlarged dropped capitals, negative indentation, capitalisation of the first word, pulled paragraphs, colour, and animation, all of which would be unsuitable for more sober and formal regulatory documents or scientific publications. These really are more the province of the graphic designer rather than the writer but are also part of writing.

Structure of an ideal paragraph

The ideal paragraph has the following structure:

- A topic sentence setting the scene for the reader
- Text developing the idea with pros and cons and mentioning any other important aspects of the arguments in the paragraph
- Text concluding the paragraph and heralding the content of the next paragraph.

The content of the paragraph does not go outside these goalposts. This is illustrated by Fig. 1 with the opening paragraph of an excellent article entitled *Algorithm for Writing a Scientific Manuscript*.¹

In the example, (1) is the topic sentence. This article is about how difficult it is for inexperienced authors to write scientific manuscripts. This claim leads the reader to assume that this article will give help with this. The idea is developed in (2): Things have changed. Greater expectations with regard to the ability to write publishable documents are now placed on undergraduate and postgraduate students. In (3), the idea is further developed:

Online writing instruction is now available. Limitations are then described in (4): Online training is not available for everyone, and many still have to fend for themselves. The paragraph finishes with further limitations and a link with the next paragraph (5): There is a lot of advice out there on writing, but so far, no-one has produced a step-by-step method. We are now going to tell you about the simple method we have devised. ‘Do not outline’ is the simple linking device to the next paragraph. From this, the reader knows that the authors are now going to report on their own experience.

The topic sentence

Despite the lack of advice on paragraphing in books and on the Internet, most guidance refers to the concept of the ‘topic sentence’. In most cases, topic sentences appear at the beginning of a paragraph; however, they may appear at the beginning, middle, or end of the paragraph:

- As the first sentence of the first paragraph, the topic sentence sets the scene for the reader, delineating the subject area of the text and the content of the paragraph. Alternatively, the topic sentence can pick up an idea from the (end of) previous paragraph, set the scene for the reader, delineating the content of the paragraph.
- When in the middle of the paragraph, the topic sentence pulls together and redirects the content of the paragraph. This is used in creative writing, but is very rare in our type of text.

- At the end of the paragraph, the topic sentence summarises the content and, if appropriate and sometimes very discreetly, heralds the content of the next paragraph.

In regulatory documents, section headers often eliminate the need for a topic sentence because they tell what the section is about.

A simple example of the way an introductory topic sentence is used to help the reader is given below. Let's assume that you wrote the following two sentences to describe the aims of a study:

The present study aimed to show that a hexavalent vaccine and a hepatitis A vaccine can be administered concurrently without affecting the antibody responses to their respective antigens. It also aimed to assess the immune response to the hepatitis A vaccine when given in a two-dose schedule at 6 and 12 months of age in comparison with the recommended schedule starting at 2 years of age with 2 doses administered 6 months apart.

Look what happens when you add a topic sentence:

The present study had two aims. The primary aim was The secondary aim was to assess

Now, the reader immediately knows that this paragraph is about the aims of the study and that it had two; this is information that they did not know until the second sentence in the original text. In flowing text as in a journal article, the reader should never be half-way through a paragraph – or even at the end – and still not know what the paragraph was really about.

Below is an example of a poor topic sentence:

Original: One of our findings was surprising. None of the 16 healthy men had measurable HPL, that is, none had more than 0.7 ng/ml serum. The same was true of the 42 patients with benign prostatic hyperplasia. None of the 20 patients with carcinoma of the prostate had HPL in their serum (8 of the 20 had been receiving stilboestrol for at least 3 months before testing, however). This did not agree with a study reported by Smith *et al.* with similarly sized groups, where HPL in the serum was detected in more than 50% of cases in each group. The differences may have been due to differences in laboratory method. Smith *et al.*

did not report whether any of their patients had been receiving stilboestrol.

The attempted topic sentence underlined in the original text promises a surprising finding – but which finding is it? Also, it is not until you reach the group of boxed words that you know that this paragraph is about the absence of measurable HPL in these three groups. The information about stilboestrol is not linked, and there is no indication of how the text is to proceed.

Restructured version: Serum HPL (limit of detection 0.7 ng/ml) was not present in the 16 healthy males, 42 patients with benign prostatic hyperplasia, or 20 prostatic carcinoma patients in our study. This was a surprising finding, because serum HPL was found in more than 50% of cases in three similarly sized groups of the same types of patients in a study reported by Smith *et al.*, and we had expected positive findings in at least some of our prostatic carcinoma patients. Eight of these patients may not have had detectable HPL because they had been receiving stilboestrol for at least 3 months before testing. Smith *et al.* provided no information on this, and we have no explanation, other than a less sensitive method or error in our laboratory, which we then investigated.

The new topic sentence (underlined) in the restructured version tells you exactly what the paragraph is about. It is clear that all this information is surprising. The information on the patients receiving stilboestrol is kept together, and the reader is discreetly led into the content of the next paragraph with the last clause of this paragraph.

Is a topic sentence always needed?

The answer to this is no. It depends on two things: the document you are writing and, especially in regulatory documents, the section of text.

In a clinical study report (CSR), for example, you will find that much greater use is made of topic sentences in the introduction and discussion sections than in the methods and results sections. This is because the introduction and discussion are the closest you will come to 'creative writing' in a CSR. The text used in the methods and results sections often incorporates many other structural elements, such as detailed section headers, flowcharts, bulleted lists, tabular lists, and tables and figures. These are often better than text; the key information in the methods or results is often in these elements

and not written out, so it's usually enough to link them and complement them with single-sentence or very short paragraphs without topic sentences.

When to paragraph and when not to paragraph

The forced grouping of a series of important instructions into an inappropriate paragraph, such as in the methods section of a study protocol, can make them difficult to find. When giving instructions, a numbered list of sentences or groups of sentences is often better, especially if you need to refer back to them. The concept of paragraphing can also often be abandoned for the efficacy results section of a CSR, except for your introductory remarks.

As an example of when to paragraph, let's look at the introductory section under the heading 'Efficacy Results' in an extract from a real CSR.

11.4 Position Original: There were notable differences between the Asian and ITT populations with regard to primary baseline subject and disease characteristics (see *Section 11.2.2*) and post-study anticancer treatment (see *Section 11.2.3*). The Hispanic sample was too small for meaningful analysis. Results for the Asian and Hispanic populations are therefore not presented in detail below. Major differences are pointed out and, for all analyses, the reader is referred to the appropriate tables in *Section 14.2*.

The results in the PP population are summarized briefly below because there were no major differences from the ITT population. For detailed results, the reader is referred to the appropriate tables in *Section 14.2*.

The focus of efficacy reporting in this report is therefore on the ITT and White populations.

The author chose to present this general introductory information in three separate paragraphs, and to gain the necessary stress on the focus of this report, presented this information in a single-sentence paragraph at the end (where it is actually likely to remain unread!). This sentence is actually a good example of a summarizing topic sentence at the end of a paragraph, but it does not serve this function standing on its own at the end. It would work as a summarizing topic sentence if the paragraph had been presented in one block, which is what we would recommend here. Terminal topic sentences can often be used as introductory topic sentences, and this is the case here, so we would have positioned the sentence before the rest of the text in one block as a good introductory

topic sentence that stresses that the focus is on the ITT and White populations. Of course, slight adjustments to the text may be necessary. Thus, we would have reformulated the text like this:

11.4 Efficacy Results (Position Restructured version): The focus of efficacy reporting in this report is on the ITT and White populations. There were notable differences between the Asian and ITT populations with regard to primary baseline subject and disease characteristics (see *Section 11.2.2*) and post-study anticancer treatment (see *Section 11.2.3*). The Hispanic sample was too small for meaningful analysis. Results for the Asian and Hispanic populations are therefore not presented in detail below. Major differences are pointed out and, for all analyses, the reader is referred to the appropriate tables in *Section 14.2*. The results in the PP population are summarized briefly below because there were no major differences from the ITT population. For detailed results, the reader is referred to the appropriate tables in *Section 14.2*.

As an example of when *not* to paragraph, let's look at the individual efficacy results that follow the above example. In the text below, four typical variables from an oncology study – overall survival, progression-free survival, time to treatment failure, and duration of response – are reported on and each has its own heading, so topic sentences describing these are not required. All sections have the same structure: an introductory sentence, a detailed extract of the results in an in-text table, and then the important messages of the table in a few brief sentences. These sentences can either be grouped in a block or as a bulleted list, or can be seen as 'stand-alone' sentences presented separately.

11.4.1. Position Original: *Table 11.18* shows the results in the ITT population.

(in-text table)

The numbers of evaluable patients, median PFS times and HRs are given below. 48 patients on Drug A and 43 patients on Drug A + chemotherapy were evaluable for PFS at the cut-off. Median PFS time was the same at 4.8 months in both treatment groups. The HR for Drug A + chemotherapy over chemotherapy alone was 0.943 (95% CI: 0.825, 1.077).

Figure 11.5 shows the Kaplan-Meier estimates in the ITT population in both treatment groups.

The reformulated version below does not combine the text or employ a topic sentence:

11.4.1. Progression-free survival time (Position Restructured version): Table 11.18 shows the results in the ITT population.

(in-text table)

48 patients on Drug A and 43 patients on Drug A + chemotherapy were evaluable for PFS at the cut-off.

Median PFS time was the same at 4.8 months in both treatment groups.

The HR for Drug A + chemotherapy over chemotherapy alone was 0.943 (95% CI: 0.825, 1.077).

Figure 11.5 shows the Kaplan-Meier estimates in the ITT population in both treatment groups.

Nothing is gained in the text from making a paragraph out of the first three sentences with a topic sentence, other than telling the reader what they already know. The approach is also often very similar in the safety section of your CSR.

A further reason for presenting separate sentences in this situation is purely practical: separate sentences make it much easier to prepare summaries or a synopsis using cut-and-paste.

How long should a paragraph be?

In novels, paragraphs often extend over more than 1 page. Unlike scientific documents, however, novels are not written to convey information to the reader as succinctly and simply as possible.

Fowler² summarizes paragraph length as follows:

... a succession of very short paragraphs is as irritating as very long ones are wearisome. The paragraph is essentially a unit of thought, not of length: it must be homogeneous in subject matter and sequential in treatment. If a single sequence of treatment of a single subject means an unreasonably long paragraph, it may be divided into more than one. But passages that have not this unity must not be combined into one, even though each by itself may seem to make an unduly short paragraph.

In most of the documentation we produce, paragraphs that extend over more than 1 page are too off-putting for most readers. As we have seen above, this is unlikely to happen, however, in our type of document simply because of the nature of

the content. Regardless, you should not let such run-on paragraphs happen in your documents.

It is impossible to say how long a paragraph should be. A reader is likely to find a page with, let's say, three visible paragraph breaks much less off-putting than one break or no breaks. This means that you should probably be going for about 2–3 paragraphs per page in a study report-type text. A journal article is very different; you should do your best with paragraphing when you prepare your manuscript, but when you see the proofs and the layout (probably in two columns), you may decide that some re-paragraphing is necessary, but it will usually not be extensive. Paragraph length for marketing and medical communications documents and websites is very different, and many more liberties can be taken than in regulatory documents, manuscripts, and textbooks.

The 'half-paragraph'

This concept is not used in English. For the 'half-paragraph', no space is left between the end of the paragraph before the 'half-paragraph' and the start of the 'half-paragraph'. This rarely occurs in texts from countries where English is the first language. It is used by authors from Northwest European countries to introduce an idea that is 'not completely new'. Even if this is a stylistically recognized concept in your language area,³ it is not a wise policy to use it in documents for international consumption. Most readers will not recognize that you want to present a related idea that is not 'completely' new. Paragraphing is difficult enough without introducing intermediate concepts!

Single-sentence paragraphs

First, a quote from *The Careful Writer* by Theodor M Bernstein,⁴ erstwhile Consulting Editor of the *New York Times*: 'An elementary school teacher told her class that a paragraph could not contain only one sentence. When the impertinent pupils asked her why, she replied that obviously if it had only one sentence then it would be a sentence, not a paragraph. That teacher deserves a sentence – and a long one'. He also says: 'A scientific paper designed to be read closely and slowly by a thoughtful audience may have longer paragraphs than a first-grade primer'.

As we have seen, single-sentence paragraphs are difficult to avoid in some sections of regulatory documents, and may even be appropriate in those

sections. They are also frequently used in marketing and medical communications texts. Generally, however, especially in journal articles and other texts, such as product monographs, single-sentence paragraphs should be avoided. One reason for this is that they attract the eye and the content of the paragraph may be overemphasized – rather like putting information between dashes in flowing text. Check this, and if the emphasis is wrong, rewrite the surrounding paragraphs. But you may want the emphasis, of course!

You may also find that it is appropriate to have a single-sentence paragraph as an introductory paragraph in a text section:

Material and Methods

We performed a retrospective electronic patient chart analysis in patients presenting to the Emergency Department of Bern University Hospital, a Level 1 trauma centre that treats about 35,000 patients per year with a catchment population of about 2 million.

Our study included patients >16 years seen over an 11-year period (2000–2011). Patients <16 years were not reviewed as they are generally seen by Bern University Children’s Hospital. All cases were extracted from ‘Qualicare’, our electronic patient management database. Reports containing the ...

A single-sentence paragraph may also be appropriate at the end of your discussion section as the conclusion:

... ..

Although all of our patients were pain-free after surgery, this does not mean that our small sample has shown that pain in Dupuytren’s disease is linked to the histological changes described. Histological examination of samples from larger samples of patients with and without pain is required, with examination of many thin sections throughout the entire specimen with special dyeing techniques for nerve fibres.

We therefore suggest that the indication for surgery in Dupuytren’s disease be extended to patients with nodules that have been painful for more than one year – even in the early stages of the disease in the absence of functional deficits – with assessment of tissue samples for histological changes in nerve fibres.

Linking words and phrases

The sentences in paragraphs and the paragraphs themselves may need to be discreetly or obviously linked. Often, the link within the paragraph will simply be that they fall within the limits set by the topic sentence – *and this is often enough in English!* Sometimes you are telling a story, so the links need to be stronger, and perhaps the strongest links are needed for contradictory statements or when a point really is being ‘argued’, with abrupt changes reflected by links such as ‘despite this’, ‘on the contrary’, or ‘whereas’.

It is easy to overdo linking words, and very often in English all that is needed is a simple ‘these’, ‘such’, ‘also’, ‘then’, ‘but’, ‘however’, or ‘therefore’. My experience is that some continental European authors use too many linking words in English in introductions and discussions. When telling your story, a dramatic build-up is usually not appropriate or necessary, so you do not need to start with ‘We did this’ and continue like this: ‘Then we did this’, ‘In addition, we did this’, ‘Moreover we did this’, ‘Furthermore we took these measures’, and ‘Finally, we did this’. ‘In contrast’, Smith *et al.* did not do this, but ‘rather’ that. ‘Notwithstanding what Smith did, we stuck by our method’.

Linking words and phrases that tend to be over-used are:

- Moreover.
- Furthermore.
- In summary it can be said that
- In conclusion it can be said that
- Notwithstanding.
- Accordingly.
- Additionally.
- In addition.
- First, Second, Third, Fourth (with and without -ly). If you use these, make sure they are not too far apart, and beware: ‘fourth’ or ‘fourthly’ should be your limit – anything higher sounds silly.
- In comparison with/to this.

Care should also be taken with ‘rather’. It is not used as a linking word in the following way in English: ‘We did not do that. Rather, we did this. Use ‘instead’, or ‘We felt that ... would be more appropriate for’, or similar.

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Improving patient communication by writing with empathy

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Abstract

Medical writers' texts are either written for specialists or for non-professionals such as patients and their relatives. Medical writers whose work is intended for patients cannot merely impart facts. They also need to demonstrate that they comprehend the patient's emotions – they must write with empathy. Empathic texts are intelligible, credible, and are written from the patient's perspective. They can help patients realistically appreciate their situation and assess the advantages and disadvantages of different therapy options. In this way, empathic writing can promote health-conscious behaviour and can foster treatment adherence.

Keywords: Empathy, Patient communication, Intelligibility, Patient's perspective, Credibility

Introduction

Medical writers' texts are usually directed toward specialists such as licensing authorities or the scientific community. Increasingly, though, medical writers also find themselves writing for non-professionals, including patients and their relatives, because decisions regarding diagnostic procedures and treatment are no longer made exclusively by physicians and therapists. In the digital and print media, patients search for and find information about pharmaceuticals and medical procedures and – armed with this knowledge – seek out clinics and medical practices that offer what they feel best fits their needs. Texts written for the purpose of patient communication can help them to realistically appreciate their situation and assess the advantages and disadvantages of the various therapy options.

Successful patient communication is especially crucial in cases of chronic illness, which result in complex, regular treatment routines over an

extended period of time. Furthermore, in some situations, treatment becomes the responsibility of the patients themselves. In such cases, effective patient communication can contribute to more health-conscious behaviour. This also fosters adherence, a factor that is often decisive for a therapy's efficacy, because patients will only adhere to the treatment plan when they accept the need for the regimen, understand how to deal with medicines and medical application devices, and are prepared for possible side-effects.

Medical writers whose work is intended for patients cannot merely impart facts, but they also have to demonstrate that they comprehend the patient's emotions and rationale – they have to write with *empathy*. That is, they have to be able to put themselves in the patients' place, have sensitivity about their symptoms, and understand their hopes and fears. But how can this be achieved linguistically? It is certainly not necessary to follow the example of Gustave Flaubert, who purportedly experimented with rat poison to be able to write the arsenic scene in *Madame Bovary*. In our article, we present the principles of empathic texts, that is, intelligibility, the patient's perspective, and credibility (Fig. 1).

Intelligibility

Intelligibility is without doubt the fundamental requirement of an empathic writing style because failure to reach patients intellectually precludes engaging them emotionally. This means that empathic texts for patients avoid foreign terminology, frequent exchange of synonyms, and abbreviations. Technical terms should be replaced by common terms or paraphrased in simple words. Patient-oriented texts consistently employ a single sentence to explain each important piece of information and thus transmit the knowledge in small



Figure 1: Principles of empathic texts.

steps so as not to overwhelm the reader. A study on the use of information booklets about cancer revealed that the information needs of patients can only be adequately met if texts are written in plain English.¹ Furthermore, research has shown that text comprehension can also be facilitated by a descriptive, lively language that uses many verbs and replaces abstract formulations like ‘minimally invasive technique’ with imagery such as ‘keyhole technique’.²

Assuming the patient’s perspective

Once the condition of intelligibility is met, there are techniques that help express empathy linguistically. The simplest is to take the patient’s position: Instead of writing ‘physicians explain the therapy options’, write, ‘Patients inform themselves about possible types of treatment’. The author thus attempts to capture the patient’s situation not only linguistically, but also in the content. This can be accomplished only if the writer constantly reflects on how patients might perceive a concrete situation, that is, what the patient actually sees, hears, and feels. The simple fact that a medicine is to be administered under local anaesthesia can be expressed, ‘You will barely feel the injection because the spot will be numbed beforehand’.

The patient’s vantage point

Certainly, a healthy person requires a high degree of psychological dexterity to be able to empathize with patients experiencing an illness and all its facets. The illness’s direct symptoms or the effects and side-effects of the treatment might not be the patient’s principal issue; often the patient’s fears or problems indirectly associated with being ill or with the treatment will be more of a concern. These fears and problems may concern relationship issues, social interactions, work, physical activity, and mobility.

Accessing self-help groups or relevant Internet forums can help writers comprehend what really disturbs the patients.

This understanding will be clear to the reader of an empathic text, particularly from the word choice. The fact is that even individual words not only convey information, but they also awaken associations. Anyone who suffers from migraines describes them like ‘attacks’ or ‘thunderstorms in my head’, and a person with a toothache refers to it using words like ‘intense’ or ‘throbbing’. Generalizing in a text about ‘pains’ or even ‘complaints’ in such cases would hardly demonstrate empathy.

Credibility

Authors striving to be perceived as empathic must be absolutely credible; they need to entirely and explicitly explain facts based on the latest medical knowledge. Explaining research results plainly yet precisely is surely one of the greatest challenges of empathic writing. Moreover, writers need to keep in mind that today’s patients want to construct their own image of the illness, prognosis, and therapy alternatives. Many patients refuse to rely on only a single authority, preferring to do their own research and compare sources; thus, patient communication texts must provide references. The vague claim that a diagnostic procedure is ‘based on scientific findings’ or that a drug ‘has been tested in clinical studies’ is definitely inadequate.

Discussion

Empathic texts should be written from the patient’s point of view. They also must be understandable and credible. In numerous ads and websites, companies and clinics describe themselves as ‘patient-oriented’ or proclaim that they practice a ‘holistic healthcare approach’. We believe, however, that proving that these claims are more than platitudes can only be achieved through empathic action, that is, with empathically written texts. Only in this way – of course followed up by true empathy in physical dealings – can real proximity to the patient be achieved.

Thus, patient communications should be based on the ideal of the helpful, empathic caregiver. Empirical investigations prove that the patients’ satisfaction with their care is determined by how the physician communicates.³ Empathy can even influence the results of therapy. For example, patients recover faster from the flu when they have an empathic physician.⁴ On the other side of the coin, insufficient empathy impedes contact with the

patient; visits that are not empathic last longer and tend to be frustrating for both the doctor and patient.⁵ The same may be true for patient texts: When patients understand the content and can identify with the language used, patient texts can fulfil their true function. When this happens, patients find it easier to comprehend and come to terms with their situation, accept their condition, and assess the advantages and disadvantages of the various treatment options. Finally, empathic texts can encourage health-conscious behaviour and foster compliance with the therapy plan.

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Author information

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Marc Esser is the founder of co.faktor GmbH, a company providing medical writing, medical education, and medical affairs support. He holds an M.D. and an M.B.A. Before founding co.faktor, he worked in clinical development, medical affairs, and marketing at Bayer Schering.

The authors offer a one-day workshop on patient communication. In addition to empathic language, this workshop also addresses aspects of graphic design and approaching patients by means of various media.

In the Bookstores



Pharmacovigilance Medical Writing: A Good Practice Guide
by Justina Orleans-Lindsay;
Wiley-Blackwell Publisher, 2012.
ISBN: 978-1119967262 (paperback).
34.99 GBP. 286 pages.

A useful reference for writing pharmacovigilance documents

Like other areas of medical writing, pharmacovigilance (PV) medical writing has many detailed regulations, guidance documents, and templates associated with it. As such, there is a need for medical writers to be familiar and up-to-date with all that is involved in preparing and writing these important documents.

The author, Justina Orleans-Lindsay, describes her book as an attempt to produce 'a comprehensive manual for all PV documents submitted to regulatory authorities throughout the life-cycle of any given medicinal product...' This is an enormous task as the number of documents that are listed in the overview of the PV documents required in the EU and US regions is large. The initial overview provides us with a side-by-side comparison of the requirements for a clinical trial authorisation and an investigational new drug submission and serves as a useful reminder that, in terms of submission documents, one size still does not fit all. Although the main focus of the book is on PV medical writing in the US and Europe, a summary of the PV requirements for Japan, Canada, Australia, New Zealand, India, Singapore, and Taiwan are provided. In general, these countries follow the International Conference on Harmonisation guidance, format and standards and each is discussed in turn in a chapter entitled 'The rest of the world'. There is also a chapter on dealing with *ad hoc* safety reviews and requests from regulatory authorities.

Most regulatory medical writers are asked to write safety-related material for documents required before and after a submission has been completed. Writers may be expected to write the whole document or contribute small sections ranging from a few lines to a complete patient narrative in a clinical

trial, through to writing some or all the sections for an integrated summary of safety or post-marketing update. The chapters of the book are organised across the drug development process: writing for clinical trials, writing for marketing authorisation, and writing risk evaluation and management plans, as well as writing for marketed products and *ad hoc* safety reviews. For many of the documents detailed in the book the author has provided the reader with a generic template containing headings and guidance about the type of information that should be presented under each heading. From a practical view, this makes it easy for a writer to track down the information required for writing specific documents when using this book as a reference text.

The chapter concerning writing for clinical trials provides detailed information on the Development Safety Update Report (DSUR). The evolution of this document is explained and placed in a useful historical context. The scope and general principles of the DSUR are outlined, together with advice on obtaining the relevant sources of data.

PV medical writing for marketing authorisation is a key area and in the chapter dedicated to this activity the author provides much insight into the main components devoted to safety in the Common Technical Document (CTD), the Summary of Clinical Safety (SCS; Module 2.7.4) and two other US-specific documents: the Integrated Summary of Safety (ISS) and the 120-Day Safety Update Report. Useful generic template models are provided for the SCS and ISS documents.

As well as describing the content of the different sections of the SCS and ISS the author proposes a timeline for planning and collating source data as well as listing key reviewers and their responsibilities. This is a useful place to start for those who have not completed these documents before. Her suggested timeline for either document is to allow up to 4 months from planning to finalisation. When a submission is planned for both the US and the EU the relevant summary documents are often completed in tandem, and it is difficult to put an exact timeline in place but depending on the scope and timing of data finalisation, 4 months is probably a minimum.

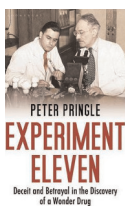
In the appendices section, there is some detail about the new EU PV legislation which came into

effect during 2012, and the author points out that for the next few years we are in a 'transition period.' To this end, she has tried to put the new EU legislation in context with a description of the revised EU legislation, and the impact it has had on other documents. For those of us not familiar with all of these changes this is a useful summary and introduction to the new legislation and will be helpful when working through this 'transition period.'

PV medical writing is considered a specialist area of medical writing by many in the medical writing profession. However, the level of involvement of a medical writer in PV medical writing often depends on the size and structure of the company, with many smaller companies requiring the medical writer to play a major part in writing most or all of the documentation. The author refers to PV medical writing 'as a discrete' discipline and separate from what she refers to as 'general medical writing'. For many medical writers this is not the case.

For those of us who consider PV medical writing as another aspect of our regulatory medical writing, there is a need to maintain current knowledge of the guidelines, templates, and requirements through continuous professional development. In my opinion, this book contributes greatly to an ability to maintain CPD in this key area of medical writing and is to be recommended.

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Experiment Eleven: Deceit and Betrayal in the Discovery of the Cure for Tuberculosis

by Peter Pringle;
Bloomsbury, 2012.
ISBN-13: 978-1408814017
(Hardback).
18.99 GBP. 278 pages.

According to the official record, the 1952 Nobel Prize in Physiology or Medicine was awarded to Selman A. Waksman 'for his discovery of streptomycin, the first antibiotic effective against tuberculosis'. That by no means tells the whole story...

In an age when the word 'antibiotic' is almost invariably followed by 'resistance', it is easy to forget what a landmark the discovery of the first antibiotics was. In *Experiment Eleven*, British journalist Peter Pringle

describes one of the earliest major breakthroughs in the field – the discovery of streptomycin.

Experiment Eleven is the rather tragic tale of a major dispute between a professor and his doctoral student. In the early 1940s, under the guidance of Professor Selman Waksman, Albert Schatz performed experiments to identify antibiotic-producing soil microorganisms that kill *Mycobacterium tuberculosis*, the bacterium that causes the then-incurable tuberculosis.

Pringle explains that, after 10 unsuccessful experiments, Schatz isolated two strains of *Streptomyces griseus* which produced an antibiotic that proved to be effective against pathogenic strains of *M. tuberculosis*. That antibiotic was streptomycin and it was a sensation. Waksman, who enlisted Merck & Co. to scale up its production, became something of a celebrity. Lots of lives were saved and some people made lots of money. Streptomycin even became the subject of a radio play featuring an Academy Award winner.

The initial manuscripts and patent were in both Schatz's and Waksman's names. But, according to Pringle, at some point Waksman decided that he wanted all the credit and more than his share of the money. He rewrote the story of streptomycin in a way that played down or ignored Schatz's contribution, while the institute at which Waksman worked, Rutgers College, churned out propaganda portraying him as some kind of philanthropist who had donated all his money to a new foundation. According to Pringle, Waksman was in reality pocketing a sizeable chunk of the cash. Schatz was getting next to nothing.

When Schatz found out what was going on, he sued. Pringle says that Waksman lied and repeatedly contradicted himself at a pre-trial hearing (described in *Experiment Eleven's* longest and most fascinating chapter), and the case was ultimately settled out of court. This settlement did not, however, alter the perception that streptomycin was largely Waksman's work and the 1952 Nobel Prize in Physiology or Medicine was awarded to Waksman alone.

Interestingly, Pringle reckons that use of the passive voice in the research papers relating to streptomycin made it almost impossible to determine who had done what. Statements indicating how each author contributed to a study are a relatively new thing and, with nothing else to go on, the Nobel Committee may have placed great weight on the fact that Waksman had his name on all the key papers (Schatz did not).

Many of the issues relating to the discovery of streptomycin remain relevant today: industry

payments to researchers; what should happen to royalties from discoveries made by academics; the struggle to publish before one's competitors; and authorship and author sequence. I laughed out loud when I read the following quotation about how things used to be from Waksman's son Byron, himself a leading scientist: 'scientists who directed laboratory programs of any significance regularly appeared as senior authors on all paper emanating from their laboratories.' In my experience, this still goes on.

PhD students often have little power in such a situation because they fear they will upset their supervisor if they complain and therefore receive a bad reference, which could damage or end their scientific career. This fear is the reason Pringle gives for Schatz going along with Waksman's demands that he sign over his patent rights. If true, it ultimately made no difference: Schatz struggled to get jobs and drifted into obscurity, performing niche research.

And that was that until British microbiologist Milton Wainwright tracked Schatz down in the late 1980s, securing an interview with him in 1989. Schatz even made an emotional return to Rutgers College, which belatedly honoured him for his work.

Pringle's picture of Waksman is not that of an outstanding, creative scientist, but of a methodical workaholic. His methods seem unremarkable and he notably failed to act when presented with a test tube containing a tuberculosis strain that had been wiped out when the tube was accidentally infected with a fungus. This was in 1935 – 8 years before the isolation of streptomycin. Much is made of Waksman's absence from the lab when the key

experiments were being carried out, but this merely reveals the author's apparent ignorance of the realities of bench research.

Experiment Eleven's opening passage is written in the style of a novel, but that style is quickly dropped in favour of one that is more formal yet still reader friendly and accessible to the lay audience. In fact, the book is quite a page turner. I became desperate to find out what, if any, redemption Schatz found and could not stop myself jumping forward to the last chapter.

Pedants among us may not appreciate the many typos and Pringle's use of 'bacteria' and 'algae' as singular nouns. And it's funny that he credits his readership with sufficient intelligence to understand the experiments he describes, but feels the need to explain what a parable and an IBM machine are. Still, one can only admire the thoroughness of his research and the great job he does of placing the discovery of streptomycin in its historical context, notably World War II and the Cold War.

Towards the end of the book, Pringle argues convincingly for the role streptomycin's commercialisation played in the expansion of R&D and marketing in the pharmaceutical industry. Major players began to adopt large-scale drug screening programmes, rushed to register what they hoped would be lucrative patents, and spent vast sums of money on advertising. These changes are, perhaps, Selman Waksman's other legacy.

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Readability of informed consent forms, sponsor participation in industry trials, and conflict of interest disclosure

Improving the readability of informed consent forms

Informed consent is a crucial feature of clinical research trials. Guidelines on developing an informed consent form urge writers to use standard plain language to provide patients with all of the relevant information they need on risks and benefits in order for them to make well-considered decisions about their treatment. Terranova *et al.*¹ conducted a study to assess, and improve, the quality and readability of informed consent forms used in cardiology. They undertook an analysis of a sample of currently used Italian and English informed consent forms used in association with seven common cardiology imaging examinations (coronary angiography, percutaneous coronary intervention, myocardial perfusion imaging, cardiac positron emission tomography, cardiac computed tomography, cardiac radiofrequency ablation, and stress echocardiography), according to the recommendations of scientific societies. As a second step they developed revised informed consent forms using reference standards (e.g. Federal Plain Language guidelines) and analysed each text for quality and readability. Quality was assessed according to three criteria: content and its organisation, text construction and layout, and development process. A readability score was estimated using various readability indexes (e.g. the Flesch-Kincaid grade level and the Italian language-tailored Gulpease level).

The results indicated that the overall quality and readability was poor in the original consent forms. They were also considered too complex and poorly organised with the most relevant information not properly highlighted. However, readability was improved with the revised forms. Although the study was small and had several limitations, it highlights the importance of writing informed consent forms that are clear and complete, which point out

the risks involved in a treatment, and are developed following recommendations of plain writing.¹

Sponsor involvement in trial conduct and reporting

There has been a lot of concern about bias and influence in industry-sponsored studies following a number of articles suggesting that industry-sponsored trials usually favour the company's product. Lundh *et al.*² investigated sponsor involvement in trial conduct and reporting of results in a sample of randomised clinical trials published in *The Lancet* in 2008 and 2009. Since 2002, *The Lancet* has requested that protocols are submitted with manuscripts; therefore, Lundh *et al.* obtained copies of study protocols as part of their analysis. For each protocol and publication, the authors extracted information on conduct of the trial and reporting, and two observers independently categorised the data according to pre-specified domains. They included 69 industry-sponsored trials and 12 trials that were industry-funded but independently conducted.

In the majority of cases, the sponsor or a contract research organisation was involved in the review and verification of information in case report forms, data entry, data storage, data analysis, and publication of the results, as opposed to these tasks being done independently by academic authors. Only two trials had a completely independent analysis. Even in the 12 independently conducted trials, the sponsor seemed to have a certain amount of influence in the conduct of the trial or reporting of the results. Medical writing assistance from the sponsor or someone hired by the sponsor was described in 37 (54%) of the studies. Lundh *et al.* suggest that perhaps it is the responsibility of journals to insist on more transparent reporting of the sponsors' role in the processes such as data processing, statistical analysis, and report writing. They go on to suggest that all journals should consider asking for study protocols and raw data to be submitted, and for independent data analysis.²

Adequacy of conflict of interest disclosure

Off-label use is the practice of prescribing a drug for an unapproved indication or age group or using an unapproved dosage or route of administration. It is illegal for pharmaceutical companies to directly promote off-label uses, but many companies have paid physicians and researchers to endorse off-label uses of their products. Using a list of physicians and researchers involved in off-label prosecutions, Kesselheim *et al.*³ investigated whether these individuals adequately disclose their conflicts of interest in the scientific publications they author. The authors collected complaints, filed by whistleblowers alleging off-label marketing, from the US Department of Justice, media reports, and other publicly available sources. They then identified doctors and researchers involved in these cases, examined their publications in the subsequent 3 years via Medline, and assessed the adequacy of their conflict of interest disclosures made in these publications.

Kesselheim *et al.* found 26 complaints claiming off-label marketing and identified 91 doctors and scientists involved. Thirty-nine (43%) of these 91 had authored 404 publications related to the drug(s) to which the author was linked in the complaint. In the complaints, these 39 doctors and researchers were alleged to have engaged in 42 relationships with the pharmaceutical company, such as being a paid speaker, writing articles, acting as consultants or advisory board members, receiving gifts/honoraria, and receiving support

funds. However, only 62 (15%) of the 404 publications had adequate disclosures. Many of these articles (43%) had no disclosure at all; 4% had statements denying any conflicts of interest, 40% had disclosures not mentioning the pharmaceutical company, and 13% had disclosures that mentioned the company but did not express the nature of the relationship between the author and the company. Adequate disclosures varied by article type, i.e. commentaries were less likely to have adequate disclosures compared to articles of original research. Kesselheim *et al.*³ argue that the results show the inadequacy of authors in preparing conflict of interest statements and suggest journal practices need to be improved.

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When peer reviewers and English collide

Please proofread the whole paper - there are several grammer and punctuation issues, MUCH better than before though - but still there.

4th paragraph - needs revision - you set up the paragraph so it sounds like youre only going to discuss post-menopause, but then start discussing pre-menapausal women.

This was followed in the same set of comments by:

Contributed by Stephen Gilliver
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The Webscout

Section Editor:

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Diabetes and psychology

You all may know that diabetes is a metabolic disease leading to secondary micro- and macrovascular complications, like nephropathy, neuropathy, and cardiovascular diseases. You may also know that these microvascular complications impair patients' daily activities and productivity and finally shortens the patients' life expectancy. But you may not know that diabetes strongly affects the patient's psychological state: patients have to cope with having an incurable chronic disease that threatens their lives. Depression, anxiety, and eating disorders are very common. These can usually be treated effectively but tend to recur. What you might also not know is that, apart from diabetes' psychological impact, it directly affects brain functions and structures, resulting in additional psychological and neurological challenges. Good mental health, I think you will agree, is vital for effective treatment; successful diabetes treatment requires not only taking medications but also a range of lifestyle changes. Diabetes management should therefore always include psychological care. The following are some excellent websites addressing the need for psychological care in diabetes.

<http://www.ispad.org/FileCenter/ISPAD%20Guidelines%202009%20-%20Psychological%20care.pdf>

This links to a PDF containing the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendations for psychological care in young diabetes patients. The paper summarises and makes recommendations based on knowledge gathered from 40 years of experience in paediatrics and also addresses topics like family dynamics and social support.

<http://journal.diabetes.org/clinicaldiabetes/v16n21998/PG91.htm>

This site describes how psychological consultancy in diabetes care is used to promote healthy behaviours via direct contact with the patient or by offering services to other caregivers like nurses. One of the leading reasons for psychological referral is non-adherence to therapy. Yet, one-third of diabetes patients at some stage of their illness will encounter psychological diagnoses like depression or eating disorders. These also affect the

patient's cooperation in managing the disease. Psychological care in general can be regarded as support for a 'sustained pro-diabetic lifestyle'.

http://www.springer.com/cda/content/document/cda_downloaddocument/9781441900302-c1.pdf?SGWID=0-0-45-1277944-p173887159

This PDF contains a book chapter that goes into detail about diabetes-related depression, anxiety disorders, eating disorders, and psychotic and bipolar disorders. The authors highlight the relevance of these psychological co-morbidities for diabetes treatment. The chapter explains that psychological disorders sometimes develop at later stages of diabetes and that diabetes also is more prevalent in people suffering from certain psychological disorders. For example, the prevalence of type 2 diabetes is higher in people suffering from bipolar disorder and schizophrenia than in the general population. This could be due to side-effects of antipsychotic medication or to physiological or socioeconomic abnormalities accompanying mental disorders.

http://www.diabetes.org.uk/Documents/Reports/Minding_the_Gap_psychological_report.pdf

Psychological care is acknowledged to be a necessary part of effective diabetes care, but has it been adopted in daily practice? Diabetes UK, a UK-based diabetes charity, conducted a survey of the availability of psychological care for people with diabetes. This report shows that about 85% of diabetes patients do not have access to adequate psychological support, and only 3% of the services provided comply with current recommendations.

<http://edrv.endojournals.org/content/29/4/494.full>

How does diabetes affect the brain? What is the clinical picture behind this? This site explains that patients with type 1 or type 2 diabetes show cognitive impairments. The pathophysiology of these impairments has not been completely elucidated. Hypotheses involve hypoglycaemia, hyperglycaemia, insulin resistance, or vascular disease.

If you have any further questions or you have any other comments or suggestions, please email me at: karin.eichele@novartis.com.

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Manuscript Writing

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Help, I can't shorten my abstract! Oh, yes you can (Part 2 of 2)

Abstracts may be the most important part of a manuscript because they are often the only part that is read and used as an information source, and because they are also used by readers and editors to decide whether to read the full article. Abstracts need to be complete, concise, and interesting. This is complicated by strict length and format limitations.

This is the second of two articles that show you how to shorten an abstract. The accent of these two articles is on preparing informational and descriptive abstracts for publications, but these considerations also apply to conference abstracts. The first article described how to shorten abstracts by eliminating unnecessary content and using plain language. This second article describes how to use linguistic devices to reduce the word count.

Use parallel construction – and get rid of 'compared to'
Parallel construction not only reduces the word count but also makes the text easier to read.

Example:

- *The time to treatment failure was 12.2 months in the treatment group, compared to 3.1 months in the group that was treated with placebo.*

can be replaced by

The time to treatment failure was 12.2 months in the treatment group and 3.1 in the placebo [or control] group.

Use incomplete phrases for the objective, design, and setting sections of a structured abstract

In a structured abstract, instead of writing out *the objective of the study was to*, you can simply start the sentence with *To* as in the following example:

- *Objective: To determine the optimal dose of vaccine X for protection against Herpes zoster in adults' ≥60 years.*

Likewise, the design and setting sections of a structured abstract can be written as phrases rather than full sentences:

- *Design: double-blind, randomized, parallel-group study.*
- *Setting: academic teaching hospital.*

Convert nominalisations to verbs

A nominalisation is a verb that has been changed into a noun. Nominalisations contain the activity in a sentence, and they are often words that end in -ment, -tion/sion, or -ing.

Because English is a verb-based language, the meaning and activity in your sentence should usually be put into verbs. Using nominalisations always leads to longer and often more clumsy sentences.

Examples:

- *Measurement of the protein concentration was made using* can be replaced by *The protein concentration was measured by*
- *Administration of the vaccine was made by intramuscular injection* can be replaced by *The vaccine was administered intramuscularly* or even better *Subjects were vaccinated intramuscularly.*

Convert prepositional phrases to adjectives

Prepositional phrases are groups of words starting with a preposition. These can usually be shortened by eliminating the preposition as in the following examples:

- *The patient had an infection of the skin* can be replaced with *The patient had a skin infection.*
- *Pain in the joints* can be replaced by *joint pain.*
- *Cancer of the breast* can be replaced by *breast cancer.* (In this case, breast is a noun being used as an adjective.)
- *Abuse of nicotine* can always be rewritten as *nicotine abuse* (again using a noun, nicotine, as an adjective).

This applies to many formulations with *of*, but it is not always possible – for example, *life quality*

instead of *quality of life* just doesn't sound right – so check this out with a colleague, if in doubt.

Avoid starting sentences with prepositional phrases; start with the subject of sentence instead

Prepositional phrases are often used to start sentences, especially by those whose first language is not English, but this often results in a long and choppy sentence. Prepositional phrases also often result in *there were* or *it is/was* constructions.

Examples:

- *By using whole body scanning in the emergency room, we saved more than 58% of diagnostic time in polytrauma patients.*

can be replaced by

Whole body scanning in the emergency room saved more than 58% of diagnostic time in polytrauma patients.

- *In 42 RA patients in 74 treatment courses, Drug A was given between 2004 and 2008.*

can be replaced by

42 RA patients received 74 courses of Drug A between 2004 and 2008.

Use plurals to eliminate articles

Example:

- *The vaccine was administered by microinjection* can be replaced by *Vaccines were administered by microinjection.*

Convert text to logical operators when possible

Logical operators are $<$, \leq , $=$, $>$, and \geq . These can replace text as in the following examples:

- The phrase *in adults 60 years of age and older* can be replaced by *in adults ≥ 60 years of age.*
- *Subjects receiving two or more doses of vaccine* can be replaced by *Subjects receiving ≥ 2 doses of vaccine.*

Use numerals instead of writing out numbers

Sometimes a sentence should be started with a number, but we often hear that numbers must be spelled out at the beginning of a sentence, or even that starting a sentence with a number should be avoided at all costs. We often feel compelled to add words like *A total of* to avoid starting a sentence with a number. However, this is not a rule, just a convention, one that we and many other medical writers

ignore, and in the end, it is the editor of the journal who will decide whether to enforce this 'rule.'

Example:

- *A total of 247 subjects were enrolled or Two hundred and forty-seven subjects were enrolled* can be replaced by *247 subjects were enrolled.*

Remove unnecessary conjunctive 'ands'

Conjunctions are words that link two parts of a sentence.

Example:

- *No treatment-related serious adverse events were reported, and no deaths occurred.*

can be split into two sentences:

No treatment-related serious adverse events were reported. No deaths occurred.

or even better

No treatment-related serious adverse events or deaths were reported.

Remove spaces between operators and symbols or numbers

Example:

- *$P < 0.0001$ (3 words)* can be replaced by *$P < 0.0001$ (1 word).*
- *Subjects >10 years of age (6 words)* by *Subjects >10 years of age (5 words).*

Compress lists

Lists can be compressed by grouping common information, but avoid using *respectively*. Using *respectively* to do this always makes the reader backtrack in your text to find out which number goes with which item in the list. This should not happen because it tires and confuses the reader.

Example:

- *The incidence of Herpes zoster decreased by 17.2% in subjects immunized with 5 μ g antigen, by 27.3% in subjects immunized with 12.5 μ g antigen, and by 55.2% in subjects immunized with 25 μ g antigen.*

OR

The incidence of Herpes zoster decreased by 17.2%, 27.3%, and 55.2% in subjects immunized with 5 μ g, 12.5 μ g, and 25 μ g antigen, respectively.

can be replaced in an abstract by

Decreases in the incidence of Herpes zoster by antigen dose were: 5 µg, 17.2%; 12.5 µg, 27.3%; and 25 µg, 55.2%.

Omit 'the' to save words

The definite article (the) is extremely important in English, and removing it can change what you mean entirely, so exercise care here. *The* can safely be omitted in some cases, and you can save some words this way as in the following example:

- *The patients treated with aspirin experienced pain relief 15.1 ± 4.2 min earlier.* In the abstract, *the patients* refers to the group of patients in the study. You will also be understood if you write in the results section of your abstract, *Patients treated with aspirin experienced pain relief 15.1 ± 4.2 min earlier.*

However, be careful when you use this type of statement in the main text of the article because *the* might change the meaning of the statement. For example *the patients* might refer to all patients or to only a group of patients, depending on the context. Also be careful when deleting *the* and *a* because this can easily cause the abstract to sound like a series of notes, so consider other solutions for shortening your abstract.

Remove unnecessary relative clauses

Relative clauses are clauses that describe and are dependent on the main clause. They often start with *who* or *that*. Using them can increase the word count and lead to more complex sentences.

Example:

- *The patients who were treated with aspirin experienced pain relief 15.1 ± 4.2 min earlier* can be replaced by *The patients treated with aspirin experienced pain relief 15.1 ± 4.2 min earlier.*
- *The values that were determined on (date)* can be replaced by *The values determined on (date).*

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The discussion section of a clinical study report

The discussion section of a clinical study report (CSR) is often a source of doubt among medical writers. The advice is usually to keep the discussion section as short as possible and not go into any deep analysis or attempt to put the trial into context. The line of argument is that the best place to really discuss the findings is in the integrated summaries, where pooled data are presented and the focus is on the big picture. And as company positions may change over time, a discussion section that is too detailed and assertive may cause problems later. The 'shorter is better' approach is no doubt sound advice that is widely applicable, particularly to CSRs that will generally be read as part of a submission. But is it always true? This is what the International Conference on Harmonisation (ICH) has to say on the matter in the guideline for the structure and content of CSRs (topic E3)¹:

The discussion and conclusions should clearly identify any new or unexpected findings, comment on their significance and discuss any potential problems such as inconsistencies between related measures. The clinical relevance and importance of the results should also be discussed in the light of other existing data. Any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies should be identified. Alternatively, such discussions may be reserved for summaries of safety and efficacy referring to the entire dossier (integrated summaries).

The first thing to note is that the guideline is not, *per se*, against actually including discussion in the discussion. There is the suggestion (in the last sentence of the above quote), in line with the 'shorter is better' advice, that summaries and overviews may be more appropriate places to compare the results of the trial with other trials. The 'such discussions' in the last

sentence of this quote is, however, ambiguous in that might not refer to all the preceding points. My interpretation is that although we should avoid making detailed comparisons of the results of the trial with other results from the programme or other results in the literature (something best left to summaries), there are still questions about trial design and conduct that may be worthy of mention. Indeed, the first sentence of the above quote says that the discussion should 'clearly identify any new or unexpected findings...', that is, are there any caveats in the interpretation of the data and are there findings that bring into question the proper conduct of the study? I think that it is legitimate to consider addressing such study-specific issues in the discussion section, and indeed, the guidelines would seem to encourage it.

It should also be noted that not all CSRs are submitted as part of an initial dossier. Some for example may form part of a follow-up measure, that is, the CSR corresponds to a study required by the health authorities as a condition for marketing approval. In this case, the CSR may well be read largely as a stand-alone document and not as part of overall dossier. In this case, the discussion should certainly address the peculiarities of the trial and, in the event that the outcomes are not as expected, justify why this might be. If the findings of the trial are not properly justified, the health authorities are likely to demand an explanation anyway.

In summary, while the discussion section should certainly not be a dissertation, there are some contexts where we should consider discussing certain study issues, perhaps even at length.

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1. ICH harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports, E3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Step 4, 30 November 1995 [cited 2012 Sept 1. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

Updated interpretations of the ICH guideline on the structure and content of CSRs

The ICH recently published a set of questions and answers about the ICH E3 guideline on the structure and content of CSRs.¹ The original ICH guideline was published in November 1995.² Just to give an idea of how things have changed since then, in 1995 few people outside academia or large companies were using the Internet and, for those that were, the browser of choice was Mosaic; WordPerfect was holding its own against Microsoft Word; the PDF format was still a proprietary format that did not support hyperlinks and other features that we take for granted these days; and XML, the 'backbone' of all electronic submissions these days did not exist. So it is a bit of an understatement to say that the needs might have changed since the guideline first became available.

The questions and answers themselves therefore focus on alignment of E3 with the requirements of the common technical document (CTD), and its electronic version (eCTD) in particular. One of the main clarifications regards the length of the synopsis. This should be three pages or less according to the E3 guideline, but as explained in the questions and answers, the ICH M4E guideline on the eCTD allows up to 10 pages on the grounds that synopses are stand-alone documents that should be intelligible without reference to the rest of the report. For complex and large studies, three pages are often far too short, however concisely the synopsis may be written. The Q&A document, however, does not disavow the three-page suggestion. Thus, as in most documents, it still seems good advice to keep the synopsis as short as possible, but without losing sleep if three pages are just not enough.

Another point addressed by the Q&A document is whether the headings in the original E3 guideline should be interpreted as a template or not. The confusion is understandable to a certain extent in that the E3 guideline contains phrases such as 'efficacy

and safety variables should be provided in section 14', which does sound like it is referring to Section 14 of a CSR, rather than a reference to Section 14 of the guideline. On the other hand, naming the title page Chapter 1 is rather absurd, and perhaps a reflection of just how keen companies are not to irritate health authorities by not giving them what (they, the companies, think) is expected. So this clarification comes as a victory for common sense.

We should also remember that the E3 guideline primarily refers to efficacy and safety studies, although it does suggest that a similar approach can be taken for clinical pharmacology studies. Both pharmacokinetics and pharmacodynamics will be a major feature of many CSRs, particularly in the earlier phases of development, so clearly sections need to be created to accommodate such results. Again, the Q&A document makes this explicit, and reiterates that the guideline should not be interpreted as a rigid template. Thus, for outcome measures such as quality of life, which were not as common when the guideline was drafted as they are now, some flexibility is needed for appropriate presentation.

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Lost causes (2)

In the September issue of MEW, Stephen Gilliver said that he couldn't tell us 'the number of times I have read the word *evidences* used as a plural noun, in manuscripts written by non-native English speakers. While grammatically incorrect ... does it impede comprehension? No.'. As further examples, I will add *toxicities* and *surgeries* to this (and there are many more). *Toxicity* and *surgery* (when used to mean a surgical operation; when used to mean physician's office practice, it can, of course, be used in the plural), like *evidence*, are abstract or uncountable nouns and therefore, from a strict grammatical point of view, should never be construed as plurals. If they are, they sound (and are) wrong. This often doesn't apply to one group of abstract nouns: those ending in '-(t/s)ion', because they are often used as countable nouns, such as *injection*, *medication*, and *revision*. As so often in English, it is difficult to give guidance on this because of inconsistent usage, especially as there are some US/British English differences. For example, *accommodations* is never pluralised in British English.

In terms of pluralisation of abstract nouns that are generally not used in the plural, there are some definite lost causes and there are some battles still worth fighting. As with any lost cause, however, you should never give up lightly, but always gracefully. I have to admit to having given in on *toxicities*. When I started work on oncology texts about 10 years ago, I vigorously defended the abstract noun *toxicity*, declaring that there is no plural (nouns ending in '-ity' are particularly resistant to pluralisation). After several years, I had to admit that the terms *dose-limiting toxicities* and *Grade 3 and 4 toxicities* have become perfectly normal in oncological texts, and that it is now silly to insist on *toxicity* because this is wasting your time and everyone else's.

I have not, however, given in on *surgeries*, and never will. *The patient had five surgeries in her medical history*. This is just too far away from what sounds correct to be acceptable. Unlike *toxicities*, I think I can still say that *surgery* is never used in the plural when it means, as in this example, *had undergone surgery five times* or *had undergone five*

(surgical) operations. And I don't think it will ever make the transition to *surgeries* with this meaning. I think it is likely that this is something that will remain wrong.

Whether things sound wrong or right is often a matter of personal taste or what we are used to hearing or reading. But some things just remain incorrect. I will never give up on deleting that incorrect 's' on the end of *informations* and *bleedings* (a patient can have *bleeds* but not *bleedings*). And *evidences* is also definitely 'not on'.

Moving away from abstract nouns in the plural, in the spirit of Stephen Gilliver's '... does it impede comprehension?', I confess that I now permit the following in oncological texts: ... *a study in patients with metastatic carcinoma of the colon who failed (on) <regimen> or failed treatment with...* Throw up your hands in horror if you wish. I know, of course, that, in our grammatical tradition, *fail* can only be used transitively (i.e. with an object) if it means *fail a test* or *an examination*. In our context you would normally have to say *failed to respond to (regimen)*. However, after having countless publications from peer-review journals held under my nose and explanatory fingers pointing to just these formulations in articles in journals, including the *BMJ*, *Lancet*, and *JAMA*, all I could say is: 'OK. I give up'. The meaning of *fail* has been extended in this context. Most cancer patients first of all respond to treatment and then, because of disease progression, no longer respond and the disease worsens. Everyone working in this field knows this, and that when *fail* is used in this way, this is what it encompasses. Understanding this is also part of accepting the use of the term in this way. I suppose that this may sometime extend to the use of *fail* with all treatments, but at present it is obviously only in this field that it has gained the currency to become acceptable. I still cannot imagine saying that a sepsis patient *failed antibiotic treatment* and don't read it in journals, even rarely.
(contributed by Alistair Reeves, a.reeves@ascribe.de)

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Points of view

Medical writing: where many talents meet – the activity seen from a scientific point of view

It all started with a friendly discussion with a colleague on giving specific pieces of advice to medical students in a course designed to help improve their writing. In a telephone conversation, I had brought up the clear difference – in *my* mind – between ‘seems’ and ‘appears’. My colleague, who had a background in English and history, said that she did not see much difference and that she had not really thought about it. I tried to explain that to me as a one-time scientist, ‘seems’ has a subjective ring to it whereas ‘appears’ has a more evidence-based slant. What I had really wanted was to tell the students to avoid the word ‘seems’ altogether in a scientific context. Certainly, ‘seems’ can occasionally creep into the discussion part of a paper but by and large it has no place in the introduction, methods, or results sections – and certainly not in the abstract.

This set me wondering about people’s perceptions in medical writing. I asked my brother, also a scientist, if he saw any difference between ‘seems’ and ‘appears’ and he replied with what I had hoped and expected to hear. ‘Seems’ describes a perceived state (thus suggesting subjectivity) whereas ‘appears’ describes an observable state (thus suggesting objectivity). He had happened to discuss it with his wife who has an academic background in English, and she had not seen any difference. This led me to wonder whether people in medical writing with different backgrounds might have different attitudes to using certain words and phrases.

It stands to reason that anyone who has *learned* medical research will not write in quite the same

way as a person who has *done* medical research. Not in the beginning in any case. In order to write as if you had *done* science requires years of experience and, above all, an open and careful mind about the world around you. Knowledge of scientific method is not enough. Knowledge of language is not enough. The two must be combined in subtle ways that assure the reader that the authors of the article (or other document) are in full control. If you write in English but it is not your first language, learning these subtleties will take even longer.

Handling even simple statistics in your daily writing work is bedevilled with pitfalls. To have a reasonable amount of knowledge of the subject is the only way to succeed, even if you have a humanities background. Otherwise there are just too many ways in which you can give the impression in your writing that you are not in control. Even when the authors have done everything right – the correct statistical considerations at every stage and the correct statistical tests – if you do not know exactly what you are writing, you can undo their good work. To write ‘the mean values did not differ’ with a *P* value is a crime against the (other) authors, when it would have been just as easy to write (correctly) ‘there was no significant difference between the means’ plus *P* value. This is a very simple example, and if we also consider the concept of relationships, i.e. associations and correlations, there is a potential minefield of ways in which the uninformed medical writer can go wrong in writing about statistics.

My bottom line is that no matter what your background may be, never stop educating yourself to think and write like a scientist.

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We received the above article from Alistair Kidd, a medical editor from Umeå in Sweden. Alistair puts forward some interesting – and controversial – ideas about medical writing that we’d like to explore in further issues, so we would be pleased to receive any comments on his article. Alistair’s

considerations about ‘seem’ and ‘appear’ prompted us to poll a few experienced writer, editor, and translator colleagues in Europe and the USA on what they think about these two verbs in scientific writing.

I summarise the responses and comments in the table below.

Name	Background	Comments
No difference		
Ingrid Edsman	Scientist	From my non-native English-speaking perspective, I don't see any difference between the meaning of 'seem' and 'appear'
Susanne Geercken	Linguist	'Seem' and 'appear' are hedging devices and have the same meaning in Alistair's example
There is a difference, but too subtle for most		
James Visanji	Scientist + Linguist	It's worth cautioning professional writers against expecting too much awareness of linguistic subtlety in other scientists. I don't think the majority of scientific writers will intentionally use one over the other to indicate a different degree of certainty
Chris Priestley	Linguist	I felt that the distinction being made contains a degree of subtlety that will be lost on most people. Whether the writer uses 'appear' or 'seem', perhaps the main thing that will be clear to the reader is that there is a (large or small) element of uncertainty or speculation involved
There is a difference and it should be preserved		
Lisa Chamberlain-James	Scientist	I totally agree that 'seems' has no place in scientific writing. At best it suggests that the author is unsure, at worst that they are hedging their bets! I'm not a massive fan of 'appears' in scientific writing either, but will concede that it does have a place if used appropriately
Laura Collada	Linguist	I do feel 'seems' is more subjective than 'appears', even if both verbs, to me, have a hint of 'not-evidence based' results. When translating these verbs, I do pay attention to this
Neil Fisher	Scientist	I would always use 'appears'. To my mind, 'seems' is in a lower register than 'appears', and 'seems' does have a subjective ring about it
Helen Frampton	Scientist	'Seems' is more subjective and gives the impression that whatever you are saying is not evidence-based. It may express a greater level of uncertainty than 'appears' and even add a negative connotation to what you are expressing
Wendy Kingdom	Scientist	I'm with the group who had never thought about it and, if asked, would not have thought there was a difference. Having read Alistair's article, I can see that there is'
Michael Schnier	Scientist	In 20+ years of teaching research writing, the distinction has never surfaced – probably due to infrequent usage. I agree with Alistair about the subjective meaning of 'seems' and the more evidence-based meaning of 'appears' which conveys a visual aspect and is generally more formal. I also concur that 'seems' – especially in the present tense – could be excluded from most sections of the journal article except for an inference in the discussion section
There is a difference but it is a matter of usage		
Gabi Berghammer	Linguist	English generally has a Latin/French-derived term and an Anglo-Saxon/Germanic term for the same concept. The difference is in register rather than in semantics. Etymologically, 'seem' derives from the old Norwegian or Germanic 'same', whereas 'appear' derives from the French 'apparoir'. French-derived terms are sometimes considered 'more learned', but using the often simpler and more straightforward Anglo-Saxon term in English generally conveys the same meaning and sometimes sounds more direct. (See also: http://en.wikipedia.org/wiki/List_of_English_words_with_dual_French_and_Anglo-Saxon_variations)
Alistair Reeves	Linguist	I have never thought about this, so it is a welcome opportunity to do so. I don't think I have differentiated in the past – and I don't think I will be doing so in the future. I don't think they convey different messages. Like Gabi, I think this is much more a matter of usage and collocation. I see no difference between 'Our findings show that X appears to be involved in this enzymatic reaction' and 'Our findings show that X seems to be involved in this enzymatic reaction'.
Not sure, have never thought about a difference		
Stephen Gilliver	Scientist	I would not use the word 'seems' in the abstract if writing a scientific manuscript, but I can't claim to be certain as to the difference in meaning between 'seems' and 'appears'

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Now let's see what Alistair has to say in response.

"Thank you for the opportunity to reply. The fact that James, Neil, Lisa, Helen, Laura, Michael, and to some extent Stephen and Wendy – several of whom have a scientific background – tended to agree with me is very encouraging indeed. Five people with a linguistic background and one with a medical background did not, but the numbers are small and no

serious conclusions can be drawn. What a pity that a scientific study with adequate statistical power will never be done!

We must not forget that many languages have only one word for 'to seem' and 'to appear' – Swedish, for example (*att verka*). Any subtlety in the difference in meaning is therefore more likely to be lost."

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Just in case . . .

'In case' seems to be used inappropriately with increasing frequency. EMWA members who attended the autumn conference in Andel's Hotel in Berlin will have seen 'Do not use elevator in case of fire'. This instruction was engraved on elegant signs beside the elevator call buttons on every floor. This use of 'in case' is also becoming more common in study documentation. For example, the instruction, 'In case of special patient groups (children, patients with dementia, etc.) describe the procedure for obtaining informed consent'. In these examples, 'in case' has been used as short hand for 'if it is the case that'. However, this short hand is not correct English and can be misleading.

'In case' implies that a contingency plan is being made. For example, 'I will take an umbrella with me in case it rains' or 'We will drive on the main road in case there is flooding on the minor roads'.

So, 'Do not use elevator in case of fire' implies that you should not use the elevator in case you get in it and find that there is a fire inside, or that your presence in the elevator might cause a fire. It would be more fluent to say 'If there is a fire, do not use the elevator. Or better, 'If there is a fire, use the stairs'. For the second example, it would be more fluent to write 'If the study population is a special patient group...'

Unfortunately, the use of 'In case of fire...' posted on hotel lifts may be a lost cause. It is far too common for it ever to be corrected. But it is still worth paying attention to this in our documentation, and an 'If ...' sentence often offers the best solution. This may be slightly longer, but the shortest solution is not always the best, even though we should always strive for brevity.

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Call for articles

Dear colleagues,

The majority of medical writers (either in the pharmaceutical industry, CROs, or as freelancers) provide documents for regulatory authorities. A smaller proportion works in the medical and health communication field writing texts for either specialised (e.g. medical doctors) or broader audiences (e.g. patients and other lay people).

In the era of 'Health 2.0', patients are empowered by information to become active and responsible partners in their own health and care pathway¹. The increasing demand for health and medical information on the web and print media has created a new niche for medical writers: medical journalism.

Medical journalists strive to inform patients and the general public about diseases and treatment options through different mainstream media outlets. These include print media like newspapers, magazines, journals, brochures, leaflets, pamphlets, as well as web-based media like healthcare portals, newsletters, blogs, e-learning, and others. One of the areas experiencing a steady growth lately is medical journalism targeted at scientific journals. Here, the requirements are quite different from those for writing for the general public.

Medical journalism is a multi-tasking profession. It requires the ability to understand complex data,

to filter these data according to (subjective and objective) relevance, and to present them in a format and language tailored at the target audience and medium (whether online or print). In most countries, the profession is not yet legally regulated. This may be a reason why the quality of medical journalism varies greatly.

From 2013 on, the Medical Journalism Column of *Medical Writing* will be focusing on techniques and skills that medical journalists need to do their job, how and where they learn them. In addition, we may report on interesting medical findings reaching the general public through mainstream media.

If you work as a medical journalist or write pieces for patients or other lay people (including children and adolescents), we need your help to transport your experience to the broader medical writers community, exactly in the spirit of Health 2.0. If you want to share your professional experience or write an article on your favourite topic, please contact Diana Raffelsbauer (diana.raffelsbauer@pharmawrite.de).

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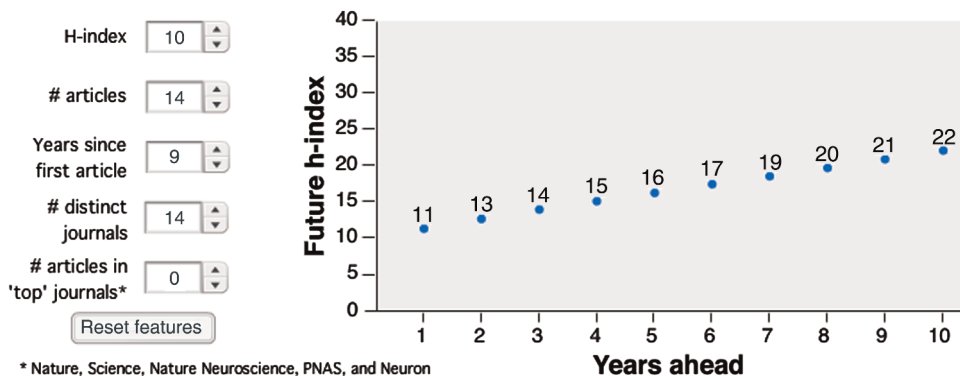


Figure 1: *h*-index prediction for Stephen Carl Gilliver

Predicting a researcher's future success

Working out who will be a successful researcher in the long term is a problem that continues to vex selection panels responsible for awarding university fellowships. It is widely acknowledged that their decisions are guided by publication metrics (measures), the most (in)famous of which is the impact factor.

The *h*-index¹ is a popular metric that grades a researcher's publication record according to the number of articles they have published and the number of times their articles have been cited. An *h*-index of *n* indicates the publication of *n* articles, each with at least *n* citations. For example, a person who has published 33 articles, each with at least 33 citations, has an *h*-index of 33.

A recent article in *Nature* by Acuna *et al.*² presents a new method for predicting future academic output based on a person's record so far. The authors created a set of formulas that estimate a researcher's *h*-index up to 10 years in the future based on the following: (1) current *h*-index; (2) number of articles published; (3) number of years since the first article was published; (4) number of different journals in which the articles were published; and (5) number of publications in 'top journals' (*Nature*, *Science*, *Nature Neuroscience*, *PNAS*, and *Neuron*). The formulas were created using data for neuroscientists, but the authors believe they are 'probably reasonably precise for [other] life scientists'. You can try them out yourself online.³ Fig. 1 shows the output for me.

The paper by Acuna *et al.* is the subject of a *Nature* editorial,⁴ the author(s) of which are clearly prepared for a backlash, inviting anyone who is outraged to 'send complaints to the usual address'. I am not outraged, but I am sceptical.

While Acuna *et al.* show that their formulas predict future *h*-index more accurately than current *h*-index alone does, the formulas were validated using data (for 1995 onwards) for individuals who are current researchers. The formulas would have performed less well if people who were researchers in 1995 had been followed for future output (since a significant proportion of them will have dropped out of research and stopped writing papers). And the assumption remains that number of publications and number of citations are good measures of a researcher's quality. Experience tells me that this is not always the case.

Over-reliance on improved computer-generated metrics would risk researchers' personal qualities being completely overshadowed. Surely nobody wants that.

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Editorial

Thanks for joining us at the EMWA Berlin Freelance Business Forum in November 2012. Meeting in person enables our medical writing community to thrive. As usual, we shared experiences, best practice, and useful tips.

The meeting minutes are posted on the EMWA website in the Freelance Resource Centre (FRC); print deadlines did not allow us to post a summary in Out On Our Own (OOOO) on this occasion.

We are currently collating the information that so many of you kindly shared by completing the 2012 Freelance Business Survey (FBS) that closed in September 2012. This survey provides information to allow appropriate fee setting for medical writing services and therefore maintains standards and

professionalism in our sector for the benefit of clients and service providers alike. We will share the 2012 FBS results with you in the March 2013 issue of OOOO.

Sam shares her experiences of migrating from the PC to Apple computing environment, from the perspective of a regulatory medical writer. Essential reading if you are thinking of making the switch!

Kath gives us some great tips for maximising the marketing potential of our websites – they are, after all, showcases for our business.

With the final quarter of 2012 in full swing and the holiday season upon us, we share Wordle.net with you – a fun tool to impress business contacts and friends alike with (seasonal) creative impact! Anu and Anders bring us another great jumble to continue that holiday mood.

Happy holidays to all and the best for a happy and successful 2013. Keep those articles coming.

Successful migration from the personal computing to Apple computing environment for regulatory medical writers

When renewing computer hardware, migration from one system to another, arguably, should not be overlooked. Some of the challenges that may be faced, by regulatory medical writers migrating from a personal computer (PC)-based system to an Apple (Mac) system, are described.

Keywords: PC, Apple, Mac, Switch, Regulatory medical writing

I had been considering and then investigated switching from the personal computing (PC) to Apple (Mac) environment over a 9-month period. It seemed natural given that I had an iPhone and the family had iPods. Incompatibilities between the calendar systems for the iPhone and the PC's Microsoft's Outlook calendar niggled enough for me to investigate a long-term solution that would allow all my devices to work optimally – together. I also wanted a quality system that would not run slower over time, and I wanted to make sure my

system was less vulnerable to external hazards such as circulating viruses – both of which had been issues with my PC.

What better way to find out if migrating was for me than to check out what Apple had to say about it (<http://www.apple.com/support/switch101/>), and then seek my own business community's advice via EMWA's LinkedIn page? So I posted my question:

'I have always used a PC for work, but am thinking of changing to a Mac, largely because all the

other hardware we have in our household is Apple – iPhone; iPods and soon, an iPad. I also hear great things from Mac desktop users. I would like to be aware of any pitfalls before I make a decision on whether to change or to stick with a PC, in terms of working in an industry of predominantly PC users. Does using a Mac create problems when sharing documents with PC-using clients? Are there functional differences in Mac & PC software that I should be aware of? I'd be glad if any medical writer out there could share their experiences so I can make an informed decision before I make my purchase.'

Before long, I was deluged with responses, mostly from Mac converts (http://www.linkedin.com/groupItem?view=&gid=2717752&type=member&item=96101656&qid=bc636391-730f-494c-9850-a977435a1fb0&trk=group_items_see_more-0-b-ttl). Overwhelmingly, it seemed that there were no insurmountable barriers to switching and that clients would see no difference. This for me was key. It seemed as though if I planned this properly, it could work for me. At this point, I should mention that I do not run any out-of-the-ordinary software programmes that others might in the medical writing world, perhaps in the medical communication or translation arena.

So, I cleared 2 weeks of calendar space and set to work cleaning my PC, and I visited the Apple store in my city. I booked a session with a business advisor, and made my purchases (Table 1, column 3). I signed up for a business package and had the Apple business team migrate as much archived material as possible from my PC to my iMac and onto the Mac platform. I bought a 3-year support package, AppleCare, that provides telephone and web support – invaluable, as one trip back to the

store with my very heavy 27-inch iMac taught me! After numerous calls to the store and AppleCare to fix issues that arose while I was fine tuning my system, I eventually found myself a senior AppleCare advisor with 10 previous years of Microsoft® experience. This individual proved my salvation where other advisors with purely Mac know-how had failed. In particular, knowledge of both systems and environments has been necessary to trouble shoot and fix issues that have arisen with migrating Outlook email and using Office on a Mac platform.

I have encountered challenges along the way that I've learned from. Mostly, I have attempted to solve these myself, but when it all becomes too much, my AppleCare advisor has been able to guide me. The lessons I've learned are described in Table 2.

Making the switch was not quite as easy as it may seem because problems became apparent over time and resolution was not always immediate. Effective implemented solutions only are described in Table 2; multiple unsuccessful attempted solutions tried along the way are not. In courting PC users to make the switch, I firmly believe that Apple must better support this specific user community. There are plenty of dedicated Mac users who have never used anything but Macs; they are well supported by Apple who knows their own platforms and systems inside-out. It's the switchers who need tailored additional support, from the point of purchase and document transfer, and continuing beyond with effective remote support delivered by individuals with both Mac and PC system-platform know-how. As an end-user, I consider that a work in progress from Apple's perspective.

Now up and running, my system works like a dream. The iMac is faster and slicker than my old

Table 1: Personal migration from a PC to Mac computing environment

Variable	PC – out with the old	Mac – in with the new
Hardware	Mesh desktop PC, 14-inch screen, purchased July 2006, subsequently regularly serviced, and upgraded twice	27-inch iMac, purchased March 2012
Operating system	Windows XP,	OS X Lion
Software	MS Office 2003 (including Word, PowerPoint, Excel, and Office)	Office for Mac 2011 (including Word, PowerPoint, Excel, and Office)
Printer	HP colour LaserJet 2840	HP OfficeJet Pro 8600 Plus all-in-one printer with AirPrint capability
Backup system	2 GB external hard drive (A5 size) – requiring manual backup	Portable 500 GB firewire drive (mobile phone size) – automatic backup of entire desktop multiple times daily via 'Time Machine'
Antivirus and system protection	AVG free antivirus and Adaware free spyware	None required

Table 2: Solving challenges in migrating from a PC to Mac computing environment and platforms

Challenge	Problem	Solution	Outcome
<i>Pre-switch</i> To avoid importing 'rubbish' from an old PC to a new Mac. You need a fresh start!	The PC is full of old documents seldom if ever used and less likely to need going forward	Clean up the PC and remove outdated files. Streamline folders. Copy these to an external hard drive	A tidy PC desktop to migrate to a new Mac. If files are corrupted during transfer, a second back up on an external hard drive is available in addition to a cleaned PC hard drive
<i>Post-switch</i> <i>Ensuring continued compatibility with a largely PC-based industry</i> To continue to work in a familiar software environment recognised as the industry norm, i.e. for regulatory medical writers, MS Office	Mac comes pre-loaded with the Apple operating system that works with Apple pre-loaded software (Pages, iWork, Numbers, and AppleMail). You will not be able to work in Word, Excel, PowerPoint, and Outlook	Buy 'MS Office for Mac' software and install on the Mac	You replicate your industry's software environment and can continue to interface with colleagues and clients as you did previously
To migrate existing MS Office documents from PC to Mac, while maintaining them in their original Windows folder/file structure	The Mac platform is different to the PC platform unless you use virtualisation software to run Windows on the Mac. If you stay with the Mac platform, folders at higher levels of hierarchy may import from PC to Mac in a different location than expected	With the PC and Mac open side-by-side, review all folders/files on the Mac for positional inconsistencies and reinstate their intended position as visible on the PC	Your documents are in the same location as they were on your PC, but you operate on the Mac platform
To ensure your colleagues and clients see the same 'Word' documents, complete with mark-ups, as you see them	Everyone seems to be using different versions of Word within the industry, and 'Word 97 for Mac' is yet another version	Save your work as both docx and doc files, circulate both and remind team members to pick up and work with the version of the document compatible with their own system	All mark-ups including 'comments' and 'track changes' are visible to all. Top tip – add your initials (and have other stakeholders do the same) to any comments and tracks to avoid loss of authorship information between different versions of Word
Joining WebEx sessions	You may need to download software to enable WebEx. If the software is not optimised for Mac platforms, then this will corrupt your system. Joining WebEx using software not optimised for Mac corrupts printer drivers, removes random pieces of external hardware (e.g. external hard drive) and some software capability. All will require removal, reinstallation, and the Mac will need to be cleaned	If you are due to take part in a WebEx session, ask if the documentation (possibly a presentation) can be emailed to you and just navigate through it on your own screen rather than through the remote WebEx session	You avoid corrupting your entire system and can still take part in the session

Continued

Table 2: Continued

Challenge	Problem	Solution	Outcome
<i>Ensuring calendar compatibilities</i> To integrate appointments and meetings generated via the MS Outlook calendar into the Mac calendar, iCal	They won't automatically integrate, so you have to manually add them to iCal	Consider winding down your use of 'Outlook' and eventually move to exclusively using AppleMail. Appointments and meetings should load directly to iCal if you respond to or generate them through AppleMail	You'll need to run Outlook and AppleMail concurrently on the Mac for a while, with the eventual aim of migrating over exclusively to AppleMail (see below)
To streamline iCal entries on your iPhone and iMac so you don't have to do a manual sync between the two devices	You keep forgetting to do a manual sync, so calendar inconsistencies may occur between devices until you remember to sync	Enable iCloud - Apple's web storage solution that stores documents, music, photos, calendars and more, and wirelessly pushes them to all your devices (http://www.apple.com/uk/icloud/?cid=mc-features-uk-g-icd-clc-icloud)	iCal on your iPhone and Mac are auto synched via iCloud. You never have to do a manual sync again. However, if the syncing seems to have 'gone off' just log into your iCloud account from your Mac and refresh - that should fix it
<i>Integrating email systems</i> To migrate email folder structure and contents from Outlook to AppleMail	Not possible - or rather, highly problematic	Consider winding down your use of 'Outlook' and eventually move to exclusive use of AppleMail. Don't remove Outlook from your Mac though	Run 2 email systems in parallel on the Mac when you first switch:
To view 'Outlook' archived emails in the original PC folder structure on your Mac	No problem as 'Outlook' should have copied onto the Mac and retained archived emails in the original folder structure	Simply view old emails using Outlook on the Mac	<ol style="list-style-type: none"> 1. Your main email system is AppleMail. Use this as your functional email from which to generate new emails 2. Use Outlook to view archived emails and to reply to old emails where you need to continue the string - remember the original content is archived here. cc yourself so that a copy goes to AppleMail and you can continue the mail string from there going forward 3. Eventually you'll use Outlook less and AppleMail more, thereby migrating fully to AppleMail over time
To keep track of your business emails while away from your desk	Potential for lost business and numerous emails waiting for you in your inbox after a spell away from your desk	Consider buying an iPhone (or indeed an android)	You keep an eye on your business wherever you are

Continued

Table 2: Continued

Challenge	Problem	Solution	Outcome
To streamline your work process so that emails dealt with on one piece of hardware (e.g. your iPhone while at the EMWA Conference) don't need to be dealt with again on your return to your desk (on the Mac)	Business emails archived on the Mac in AppleMail don't show up in the iPhone email folder structure	Check your business email account settings. It may have been set up as a POP account. This type of account just shows emails on the device from which you access your emails and doesn't allow them to be replicated on your other devices. Now migrate your POP business email account to an IMAP account. This type of account allows emails and their folder structure to show on all your devices. Make sure that within AppleMail, your business email archive folders are set up in your business email master folder, and not in the master folder called 'On my Mac'. Once they show in your business email master folder, they automatically show up on your iPhone	You are IMAPed! Keep your iPhone emails tidy, or your Applemail emails tidy on the Mac – but you'll never need to do both independently again! You may need to buy more webspace if you have a private email domain because your email folders now take up space on the server. Remember to clean out sent mails and deleted mails regularly to maximise use of available space
<i>Bookmarked internet pages</i> Migrating bookmarked 'Internet Explorer' pages to 'Safari' on the Mac	You forgot to mention that you need to retain bookmarked or favourite pages when the PC to Mac migration was done!	There's no shortcut that I could find! With the PC and Mac open side-by-side, review all your web browser bookmarks or favourites on the PC and find them again and bookmark them on 'Safari' on the Mac	You might well be able to include this in your migration, so remember to ask at the outset!
<i>Security</i> Choosing an antivirus for your Mac	You don't need to! Mac is designed in a different way to PC. In lay terms: the house is built with locked doors and windows, rather than open doors and windows, so fending off intruders is not an issue		No further expenditure on antivirus; no keeping antivirus updated
<i>Backing up</i> Keeping your entire system backed up		Use Apple's 'Time Machine' which captures a copy of your entire hard drive to an external hard drive	If you lose (a) document(s), you can search back through Time Machine to find and reinstate it. When you are away from your business, you can disconnect and store the tiny external hard drive that Time Machine backs up to in a safe place

PC; it has a beautiful user interface and the super-size screen makes working with multiple documents a breeze. It has some wonderful (and, so far, foolproof) pre-loaded software for film making and showcasing photos – a boon for the family.

So would I do it again? Yes, but I'd block out more work-free time (3–4 weeks) to make sure my system is working smoothly before resuming work. Compatibility is still an issue at times, but I am now aware of the danger of blindly implementing a suggested software download. I have support on the end of a phone with my personal Apple advisor who understands both the PC and Mac

worlds. There are also numerous Mac forums for ideas on how to approach a particular problem when my advisor is not immediately available. I feel more computer-savvy now and am more likely than the pre-switch me to attempt to solve problems before seeking help. In a regulatory medical writing arena, migrating from a PC to Mac computing environment, although initially labour intensive, has been overall successful in this freelance medical writer's opinion.

Sam Hamilton
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Medical Writing Jumble # 5

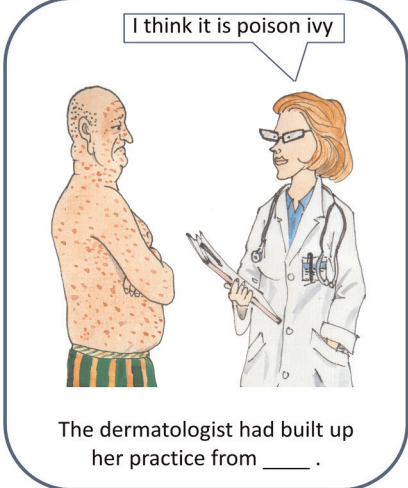
1. Rearrange the jumbled letters to get a meaningful word related to medical writing.
2. Next, take the circled letters from each word and make two new words that will answer the riddle in the cartoon. Hint: The answer is probably a pun.
3. Use British English.

INCICL ○ □ □ □ □ ○

OMRIN □ □ □ □ □ ○

ESTLCE ○ □ □ □ □ ○

UNAMH ○ □ □ ○ □



I think it is poison ivy

The dermatologist had built up her practice from ____.

Answer: □ □ □ □ □ □ □

by Anuradha Alahari | Illustration: Anders Holmqvist See page 332 for the answers.

The Toolbox: Wordle It

www.wordle.net/ is a great tool created by Jonathan Feinberg. With the seasonal holidays nearly upon us, you might like to try it out. It's great for those business Christmas cards, or even the personal variety.

Create 'word clouds' from text that you type in to the 'create' box. The generated clouds give prominence to words appearing more frequently in the source text. The clouds can be formatted with various fonts, layouts, and colour palettes. You can share them with your friends and colleagues, or save them to the Wordle.net gallery for public sharing.

Here are a few tips to get you started:

1. Create your source text in a Word document on your hard drive. Then, copy and paste it into Wordle. That way, if you want to tweak your word cloud, you won't need to start typing in the source text from scratch as you develop your cloud.
2. Once you have generated your word cloud, print the screen to your desktop, and crop the resulting image. You can paste this into emails, or any other type of document, and share it.
3. Scour the Wordle gallery for publicly shared word clouds. Picking up a readymade one

may be less fun than making one yourself, but can save time. Or just be inspired...and start creating!

Here are suggestions for uses:

1. Business or personal seasonal or holiday greetings cards.
2. Teaching - tried and tested for EMWA foundation workshop Standard Operating Procedures (SOPs): Processes and Authoring by Sam Hamilton and Tracy Farrow. We created clouds of words associated with poorly- and well-written SOPs.
3. Marketing your business - communicate effectively with your target audience using relevant words, perhaps translated into their language, to give a personal touch.

This is the word cloud I created to market my business. I chose the same colour palette as my logo for consistency and continuity.

So what are you waiting for? Get Wordling!

Sam Hamilton

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Websites: Maximising Potential

Many freelancers now have their own websites. Designed correctly, websites are a great marketing tool for your business, attracting new clients and keeping in touch with your current client base. Here are some tips for maximising your website's potential.

1. Search engine optimisation is the term given to improving your website's visibility on the internet. Think of the key words that people might use when looking for a medical writer, and include these in your website text, including text relating to images on your site.
2. Websites are a form of advertising so consider your target audience with regard to your choice of images, visuals, and text. Ensure the text is accurate with respect to spelling and grammar and take time to align text and images so the overall picture is pleasing to the eye. If you can't get these simple things right, potential clients may wonder what else you may get wrong.

3. While you want to get information across, don't make your website too 'wordy'. Use pictures to create interest and white space to rest the eyes - reading from a screen, particularly on phones, can be tiring.
4. Make it easy to navigate around your site. Use clearly marked tabs and internal links to other pages on your website. Don't bombard your reader with highly detailed information all at once - enable them to 'drill down' or navigate to the detail as required.
5. To increase traffic to your website, see if you can persuade other related businesses to put a link to your site on their website, and return the favour.
6. Writing a blog can also increase traffic and your visibility through search engines because it gives you the opportunity to regularly update your site's content. It's also a fantastic way of keeping in touch with your clients.

Kathryn White
Cathean Limited Medical Writing Consultancy, UK



Answers to Medical Writing Jumble #5:
CLINIC, MINOR, SELECT, HUMAN
The dermatologist had built up her practice
from SCRATCH.