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CASE REPORTS IN THE PAST, PRESENT AND FUTURE

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IN THE BEGINNING

For most of history, illnesses were only broadly defined as fevers, fluxes, and other maladies, so that one illness was often confused with another. This all changed when the 17th century English physician Thomas Sydenham started to classify diseases according to their symptoms, signs and clinical context. Sydenham was the first to attempt to identify and classify particular diseases in the same way his contemporaries in the Royal Society were identifying and classifying plants, animals, and minerals. This allowed physicians to become accurate diagnosticians, and enabled them to recommend appropriate treatments and predict the patient's likely response and outcome[1]. Scientific publishing began in 1665 in the Royal Society's *Philosophical Transactions*. Its reports went through four distinct stages: simple reports of events (1665-1700), arguments over the results (1700-1760), discoveries claimed to explain unusual events (1760-1780) and reports containing experimental proofs (1790-1800). It was not until the early 18th century that medical articles began to appear. Early on these reports were observations of single patients (i.e., case reports) but by the end of the 18th century most papers described groups of patients suffering from a defined disease. In 1731 the Edinburgh Medical School published *Medical Essays and Observations*, which in 1733 became the peer-reviewed *Edinburgh Medical Journal*. The *Lancet*, which published lectures from the London medical schools and case reports, first appeared in 1823[2].

By the close of the 19th century advances in anatomy, physiology, biochemistry and pathology were applied to medicine by pioneering Austrian and German physician-scientists such as Virchow, von Recklinghausen, Traube, Wunderlich and Kusmaul[3]. These events had a major impact on William Osler, a young 23-year-old Canadian doctor, who went on to introduce the German concept of "Innere Medizin" (internal medicine) to the English-speaking world and was one of the driving influences behind the development of the modern hospital[4,5]. Osler was the first Physician-in-Chief of the Johns Hopkins Hospital from 1889 to 1905, where he advised his students to *"Always note and record the unusual. Publish it. Save it on a permanent record as a short, concise note. Such communications are always of value."*, and believed case reports were essential to medicine and patient care[6]. At that time just over 150 fatal diseases had been defined and classified by the French statistician and demographer Jacques Bertillon. This was an age of optimism when every doctor was a scientist, and major discoveries and breakthroughs were made faster than they could be broadcast. Case reports of unusual cases were identifying new and clinically important conditions so that Bertillon's *Classification of Causes of Death* required frequent revisions. In 1898 this classification was adopted by the American Public Health Association and subsequently became the *International List of Diseases (ICD)*[7]. Since this now contains more than 120,000 diagnostic terms, it has become less and less likely that a single report of an 'unusual case' will reveal something not previously known, which is both important and clinically relevant. Nevertheless, up to 1976 a substantial number of medical articles were still case reports[8]. Around this time, prior to the emergence of HIV and COVID-19, many had come to believe that there was nothing valuable left to be discovered at the bedside, and that in the future all big medical advances would be made at the scientific benches of high-powered institutions.

THE DECLINE

By 1980, editors of many medical journals had embraced the concepts of evidence-based medicine and started to

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consider case reports as weak evidence and non-scientific. Increasingly they favoured the publication of large randomized controlled trials[9]. Many trials are funded by pharmaceutical companies who promote them extensively and for this reason they are likely to be frequently cited, which greatly increases a journal's impact factor. In contrast, case reports are seldom cited, so that their publication potentially lowers a journal's impact factor and prestige. As a result, most major journals either stopped publishing case reports or only accept those of exceptional quality, novelty, interest and relevance[10].

Nevertheless, there is still a place for case reports of unusual clinical observations[11]. Adverse effects can result from the use of new medications and new technology, but also there may be unrecognised benefits from their 'off label' use. As the recent COVID-19 pandemic illustrated, new diseases are emerging and when they first appear case reports are the only way evidence on them can be gathered. Case reports offer an opportunity to *learn from errors*. System errors are major challenges for modern medicine, as common diseases are often missed or mismanaged because of unusual presentations, or flawed processes of care, or misleading, misinterpreted or inappropriate investigations, and discrepancies between ante-mortem diagnosis and post-mortem findings[12].

THE RENAISSANCE

The reluctance of medical journals to publish case reports had consequences, especially for young doctors. Many present-day clinical scientists started their career by publishing a case report. They had seen an interesting or unusual case, researched the literature, presented it to their colleagues, then wrote it up and tried to publish it. If successful another notch was added to their curriculum vitae as they tried to climb the next rung of the academic ladder. Case reports had been the easiest and cheapest way to get published, and one or two publications have traditionally been considered the entrance requirement to academic medicine. Moreover, prior publications are often the only way to get support for a research project. In response to this demand from aspiring young academic clinicians the number of journals that publish case reports has increased. Most of these are paperless open access journals that have an article processing charge (APC). Many have high acceptance rates and there are a number of questionable publishers that mislead researchers regarding fees, peer review, and academic credentials[13]. In 2014, the *European Federation of Internal Medicine* (EFIM), at the request of young internists, launched the *European Journal of Case Reports in Internal Medicine* (EJCRIM) as a sister publication to European Journal of Internal Medicine (EJIM). It is a not-for-profit electronic open access journal, which provides a forum for internal medicine doctors to report interesting cases or a series or cluster of cases. It has a 40% acceptance rate *(Fig. 1)* and an average editorial turnaround time from submission to publication of approximately 40 days *(Fig. 2)*. The APC of EJCRIM has been kept as a low possible; as an online open access journal the main costs are confined to administration, proof reading, type setting and obtaining a digital object identifier (DOI) number *(Fig. 3)*.

WHY WRITE A CASE REPORT?

Before writing a case report, consideration should be given to its likely audience. Fifty years ago, as a young doctor in training, I religiously read the Lancet, New England Journal of Medicine and the British Medical Journal from cover to cover. I no longer do this. Instead, every time I encounter a clinical problem, I look it up electronically using the internet. Even as editor of EJCRIM I have no illusions that colleagues are browsing its pages on a regular basis. Of around 110,000 case reports from the journal's website looked at each year, most are probably because doctors or their patients are looking for information to help them solve a problem.

A case report should not be confused with a case presentation. A case presentation, such as made to colleagues at a hospital grand round, may be interesting, educational and entertaining. They often take the form of a detective mystery, where all is revealed by the pathologist, accompanied by cheers from the audience who got it right and moans from those who got it wrong. In contrast, the purpose and important message of a case report must be clear from the title, it should be flagged in the introduction, explicit in the report, and repeated in the discussion. Most importantly, the title should contain terms that search engines can find. For example, the Google search algorithm is unlikely to find a case report on Behçet's disease entitled 'The long and winding Silk Road'.

A case report demonstrates the authors' academic knowledge, logical critical thinking and hypothetico-deductive reasoning. Traditional medical education emphasised rote learning and had an artificial separation between teaching in the basic sciences in the early years and teaching in the clinical sciences in the later years. As a result, acquiring knowledge in a clinical context or to appreciate its relevance or irrelevance only started after qualification when the practice medicine finally began, and clinical competence was gained haphazardly through trial, error and self-directed learning. Fifty years ago, problem-based learning (PBL) was introduced to address these issues by Canada's McMaster University. It is now used by hundreds of medical schools throughout the world[14]. PBL is a highly structured process that obliges students to use their existing knowledge and to acquire new knowledge to solve clinical problems. All case reports should follow this process as they begin with an interesting clinical encounter, which prompts the authors to think and apply what they know already and then seek new knowledge. The area of interest for further enquiry should be identified: is it an uncertain diagnosis, doubt about management, an unexpected outcome, or something else? This should be followed by a literature search. Arguably, the most significant advance in medicine in the last 50 years has been ready access to the literature. Any doctor, anywhere can now access on his phone multiples

of all the medical literature available in most medical school libraries a generation ago. Therefore, there is no longer any excuse for not performing an adequate literature search. Once this search is completed, the authors must decide if their case is still of interest, not only to themselves, but also to others.

HOW TO WRITE A CASE REPORT

Firstly, the main message of the report (its *learning points*) should be defined and captured in the title. Secondly, a case report is about a patient, and the patient should be described. The description should not just include the patient's symptoms and signs but also their context. In addition to age, sex and ethnicity, context includes anything else that is clinically relevant. For example, if infection is possible then exposure (including to animals), prior blood transfusions, occupation, sexual and travel history should be provided. If the patient is very sick, then report if he or she can eat, get out of bed, think clearly, and vital sign values. Do not just provide a tedious list of investigations, but provide a rationale for why and when they were performed.

Many authors use a case report to strut their diagnostic prowess. Indulging this vanity is seldom appreciated or warranted as in the era of 'scan when you can' making a diagnosis is usually not too difficult, whereas how to treat 'a patient like this' and what happens to them subsequently is often far more instructive. Make sure you report details why and how the patient was managed, and what happened to them. Rather that reporting a case immediately after discharge, it may be wiser to wait a few months so that more information on the patient's outcome can be provided.

HOW ARE CASE REPORTS ASSESSED?

In 2013, the Consensus-based Clinical Case Reporting guidelines for case reports were published[15]. It is a 13-item checklist, which includes title, key words, abstract, introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic interventions, follow-up and outcomes, discussion, patient perspective, and informed consent. Unfortunately, this list does not contain a requirement to explain why the case report is important and should be published. If this is not made clear it is inevitable that the importance of a report, and it chances of acceptance, can only be judged by the reviewer's subjective opinion.

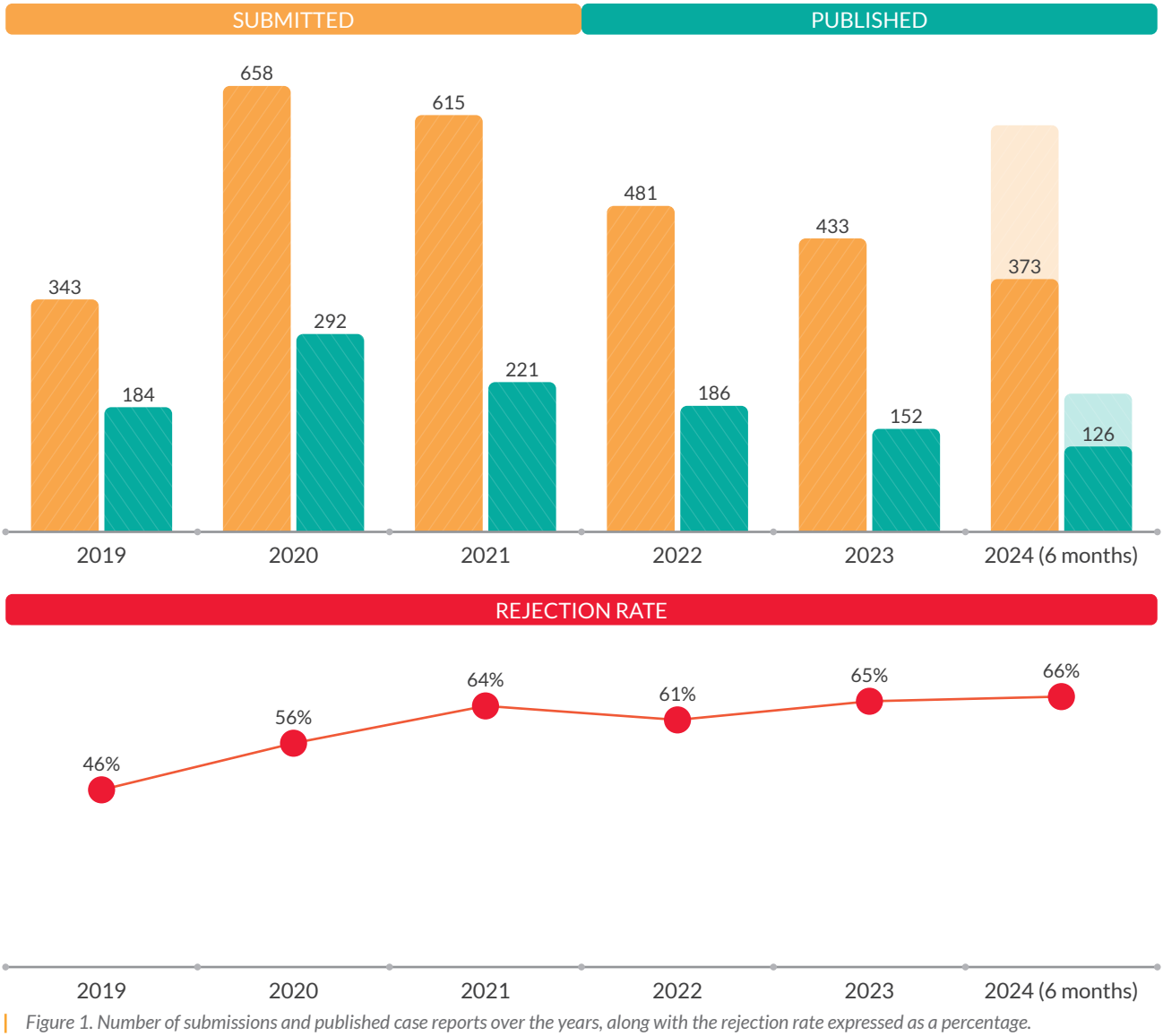


Figure 1. Number of submissions and published case reports over the years, along with the rejection rate expressed as a percentage.

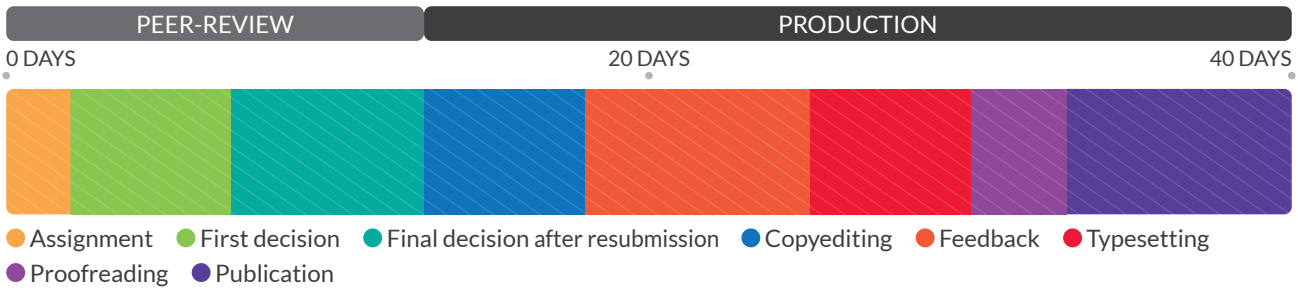


Figure 2. Average turnaround time of the editorial process from submission to publication related to the year 2023.

In order to make the assessment of case reports less subjective Ramulu et al.[16] developed and validated a case report review instrument. The four variables with the highest agreement between the validating reviewers were: (i) rationale for writing the case report; (ii) implications of the case report; (iii) adequacy of the literature review; and (iv) overall impression about whether to accept or reject the manuscript. These findings agree with my own 10-year experience as Editor-in-Chief of EJCRIM and how the journal's reviewing process have evolved over the years. Initially it had been hoped that all articles would be peer reviewed, but this became impossible as the number of submissions increased. Therefore, all papers now go through a preliminary screening process.

First, the report must pass Socrates' triple filter test: is it *true*, is it *good*, and is it *useful*? (*Fig. 4*)[17]. According to Plato, Socrates considered goodness to be analogous to the sun, as it allows us to see. Therefore, for a case report to be 'good' it must be *illuminating* (i.e., enable something to be seen for the first time, or more clearly). Surprisingly, many reports are rejected because claims made by the author are not true. Despite easy access to nearly all the peer reviewed medical articles ever published provided by MEDLINE, Google, etc., many authors fail to search the literature adequately. Today, the phrase 'to the best of our knowledge' is worthless and should be replaced by the terms used and other details of the literature search on which the authors' knowledge is based.

The commonest reason for rejection is that the report contains nothing new and is not illuminating or interesting and provides *no learning points* – it does not report something that makes an aspect of medicine clearer or provides a valuable lesson for other clinicians. Before writing a case report, authors should be clear in their own minds what its 'learning points' are. What exactly are they trying to teach? The fewer the learning points, and the more concisely they can be clearly expressed, the more likely a report will be accepted. Once the learning points have been identified, the next step is to determine if they are novel or already well established. Many authors submit case reports with a literature review. However, a case report of a condition that already has a substantial literature associated with it, is unlikely to merit publication. There is no point publishing information that is already well known and available in standard textbooks. Therefore, the policy of EJCRIM is not to publish reports that provide no additional information to that available in *Uptodate*®[18], the widely used electronic medical encyclopaedia. However, the journal is very interested in credible reports that coherently contradict or question current knowledge.

The final screening step is to determine if the report is useful. For a case report to be useful its findings must be able to be used for a practical purpose or in several ways. Many authors give long rambling speculative explanations of why their single case report generates a complex implausible hypothesis and is, therefore, useful. To paraphrase Occam's razor, if it is not simple and obvious it is probably not useful.

Once this screening process is over, some reports are accepted without review because it is clear they are true,

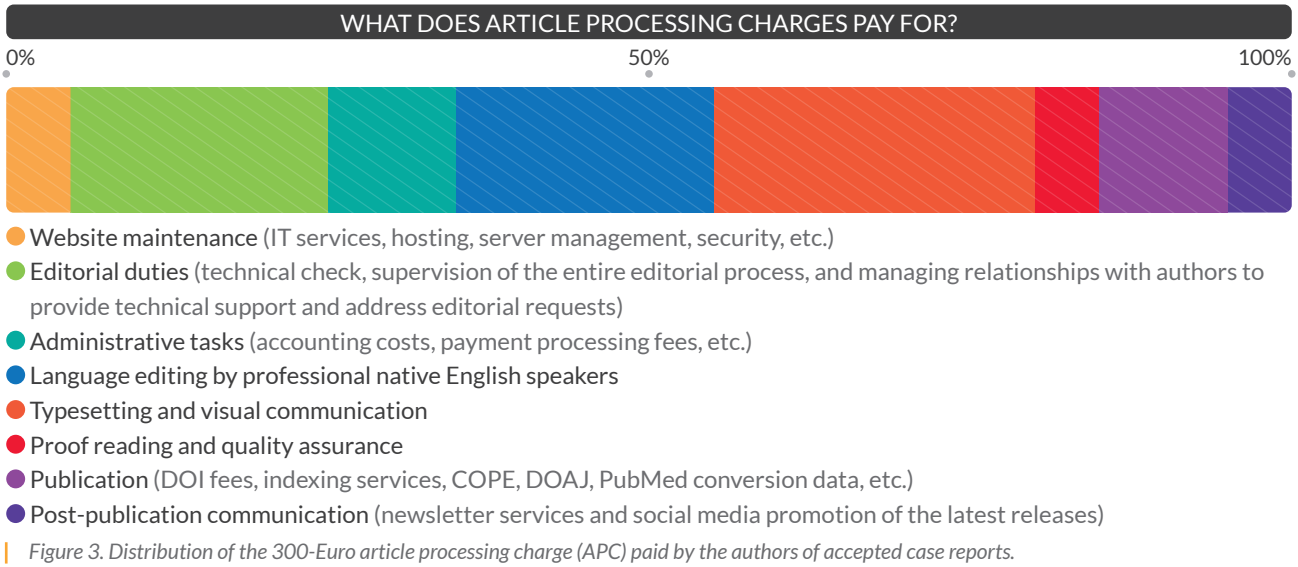


Figure 3. Distribution of the 300-Euro article processing charge (APC) paid by the authors of accepted case reports.

illuminating and useful, while some are immediately rejected because they are not. The remaining papers are peer reviewed because they are still of interest, but not possibly for the reasons suggested by the authors.

WHY ARE CASE REPORTS THAT ARE ARE NOVEL AND TRUE STILL REJECTED?

Bad medicine

EJCRIM rejects papers to protect both its own reputation and the authors'. It is not in anyone's interest to publish a paper that costs the authors money and may potentially do them more harm than good. Some reports display major errors in clinical practice, unappreciated by their authors. For example, performing a kidney biopsy on a middle-aged farmer with renal failure and jaundice without first considering leptospirosis. Such a report might have been of interest if the learning point had been that this was an error that should have been avoided and not the claim that leptospirosis is a rare condition. Similarly, two reports fretting over puzzling histology on lymph node biopsies, one from a teenager and another from a goat farmer who both presented with fever and fatigue, were of little value as the first patient had infectious mononucleosis and the other brucellosis, and a lymph biopsy was never needed.

Rarity alone does not justify publication

Although a large part of the evidence-base for rare diseases can only come from case reports, spanophilia, or love of the rare, was one of the seven sins of medicine described in a landmark article by Dr Richard Asher published in 1949[19], and rarity alone does not justify publication. Over 6,000 ICD diagnostic codes refer to extremely rare conditions, which only occur in 5 to 80 per 100,000 of the population, so that a single rare condition is unlikely to ever be encountered within the lifetime of a practising physicians. Therefore, for the learning point of a case report of a rare condition to be that 'every physician should always think of it', is a fatuous platitude. Nevertheless, although each individual disease is rare, the prevalence of rare diseases in the general population is 3.5–5.9%, so that currently 263–446 million of the world population are estimated to be suffering from one; more than 70% are genetic, 70% are diagnosed in childhood, and many of them result in early death[20].

The study of rare disease is now an active area of scientific research with its own dedicated journals such as the *Orphanet Journal of Rare Diseases*, which also publish case reports. Many patients with rare conditions can spend years under expensive medical investigation before they are correctly diagnosed. Much of the research of the rare diseases scientific community is directed at shortening this diagnostic odyssey and making it cheaper, and also improving prognostic predictions, genetic counselling, treatments, and providing better supportive care[21].

When reporting a rare condition authors should consider what someone with the condition, or their physician, would want to know about it. The main value of case reports of these conditions is not to confirm what is known already, but to add new information. The diagnostic criteria of a rare condition are usually well described, whereas often little is known



Figure 4. Socrates.

Necessary causes
• If **X** is a necessary cause of **Y**, then if **Y** present **X** must have been or is present. • BUT the presence of **X** does not mean **Y** must occur. *(e.g., tubercle bacilli is a necessary cause of tuberculosis)*
Sufficient causes
• If **X** present **Y** will occur. • However, there can be other causes of **Y**. *(e.g., a head injury may be all that is needed to cause death, but there are other causes of death)*
Contributory causes
• A factor that is a contributory cause among several other causes. *(e.g., poverty and malnutrition are contributory causes of tuberculosis)*

Table 1. Types of causal relationships in disease development.

about variations in presentations, outcomes and responses to treatments. Yet invariably authors neglect to report what makes their patient different from those described already in the literature or what happened to them.

Conflating coincidence with association and association with causation

Many case reports are of two rare conditions occurring together, claiming an association which has never been seen before. When two things occur together it is more likely to be a coincidence than an association. If two rare conditions occur in 1 per 10,000 of the population then the chance of them both occurring together is 1 in 100 million, which makes it very unlikely they will ever be seen together again. Therefore, it is pointless proposing a hypothesis that tries to explain why this coincidence occurred or why it might be an association; to do this a series of cases is needed. One of the reasons rare conditions are not commonly associated with other conditions is because they usually shorten life expectancy so that the patients die before the common diseases of aging can develop. However, the recent advances in genetic technology have made it possible for patients with a rare disease genotype to be identified when the clinical phenotype is not present. Therefore, there a need for so-called "reverse phenotyping" to correctly establish the full phenotype of many rare diseases[22]. Hemochromatosis, for example, can often be detected in the elderly who have little or no clinical evidence of the disease[23]. Such cases are of interest as they identify knowledge gaps about the prognosis and appropriate management of these conditions, and (possibly) previously unrecognised associations with other conditions.

Association is not the same as causation. **Causation** is when one event, process, state, or object (a **cause**) contribute to the production of another event, process, state, or object (an **effect**). Usually, an **effect** has many causes, which could be *necessary*, *sufficient*, or *contributory (Table 1)*. Bradford-Hill[24] identified those aspects of an association that make causation likely. Similarly, Naranjo et al.[25] developed a simple score to estimate the probability that a drug caused an adverse clinical event. The Bradford-Hill criteria or the Naranjo score should be used to support any claims of causation.

Bad writing and carelessness

Good writing should be clear, brief, easy to read, and interesting. To find out if the paper is interesting ask a friend or relative to read it and give an honest opinion. Beware of exceeding the recommended 1,500-word limit. The fewer the words used, the less need to be corrected. EJCRIM does employ proof readers who will correct minor errors in a short report, but not if it rambles incoherently for page after page. Provided they are set to the appropriate language, modern word processors correct spelling and grammatical errors, and it is careless not to use them. Abbreviations should be avoided, because they make a paper more difficult to read and understand: they should not be used in titles, abstracts or learning points. Some reports, such as those of system errors, may expose the authors to liability and litigation. Therefore, before submission case reports should be shared with the patient and consent obtained. Authors should read the reviewer's comments and respond to them, and re-submit copies of their paper with the revisions clearly marked. Unless asked for a very minor change, it is unwise to re-submit within a few hours, without reflecting and adequately addressing the changes asked for, especially if a major revision or complete re-write of the paper has been requested.

CONCLUSION

To be accepted by EJCRIM a case report does not have to be outstanding, but it does have to be true, illuminating, useful, interesting, and easy to read.

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