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Systematic Review

Evaluation of the Relevance of Research Articles Published 50 Years Ago in Key Scientific Journals in the USA, England and Germany: Introduction of 50 Years Impact Index in Addition to Impact Factor

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Abstract

The aim of this study was to assess the current applicability of articles that show important advances in medicine. The recruited papers include those published fifty years ago in the most respected journals in the USA, England and Germany. Using PubMed Central citations since 2010, original articles closely related to papers published in 1966 in the New England Journal of Medicine (NEJM), the Lancet and the Deutsche Medizinische Wochenschrift (DMW) were identified. In the NEJM, there were 163 observational articles, 18 clinical, and 117 case reports. In the Lancet, there were 390 observational articles, 29 diagnostic, 82 therapeutic, 38 animal, 28 *in vitro* studies and 61 case reports. In the DMW, there were 77 observational articles, 39 therapeutic, 28 diagnostic, 7 animal, 4 *in vitro*, 9 other studies and 57 case reports. The number of highly relevant articles still currently cited were determined as 12/298 (4%) in the NEJM, 11/ 628 (1.7%) in the Lancet and 1/221 (0.45%) in the DMW (0.45%). It was concluded that "half-hundred years impact index" should be regarded as a measure of 'relevance and quality over time'. Combined with impact factor, it could be a better indicator for importance of scientific journals.

Keywords: Journal impact factor, Medicine, Publications

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Introduction

The progression and speed of science differ at various points in time in an unpredictable manner. Although the important factors indicating progress remain obscure, any novel information or technology can suddenly change the research direction and rapidly decrease the usefulness and importance of previously established knowledge or methods. For example, modern imaging systems introduced during the last three decades have reduced the importance of clinical examination, such as palpation, percussion and auscultation and thus, their practicability and validity. The metallic and half-metallic diagnostic instruments used in the early decades of the last century for endoscopy of the respiratory and upper and lower alimentary tracts have been replaced by flexible fiberscopes, which are used today not only for diagnostic but also for therapeutic procedures.

In the last two decades, the impact factor has become an important criterion for judging the relevance and importance of scientific journals. However, how to assess the impact of a specific publication over long time remains unclear. The aim of this study was to identify papers published in the most important journals in clinical medicine that retained relevance for half a century. Current relevance was also judged by the number of citations between 2010 and 2018 (CT_9) and during the last half-hundred years (CT50). The most important journal in each of the three countries (namely, the New England Journal of Medicine [NEJM) from the US, Lancet from England and Deutsche Medizinische Wochenschrift [DMW) from Germany] published in 1966 were used to identify relevant articles. Using these data, we developed a new measure of 'relevance over time' or 'the half-hundred years impact index' that could serve as an addition to the impact factor of scientific journals.

Indexed Papers

In each weekly issue of the NEJM, four to seven original articles were published together with other publications including case reports, review articles (reported in the "Medical progress" category), diagnostic or therapeutic articles (under the title "Medical intelligence"), "Special articles" in various fields (including fields unrelated to medicine), weekly clinic-pathological reports, and various notes on medical law and other subjects. Additionally, each

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issue contained detailed comments on relevant original articles, short correspondence notes, reports of medical societies and other information.

In each weekly issue of LANCET, seven to eight original articles, short scientific research articles under preliminary communications, other review or leading articles under annotation, points of view or special articles or hypotheses as well as letters to the editors and various articles not related to research were published.

In each weekly issue of DMW, five original articles, one article on actual diagnostic and one on actual therapy of a specific disease, one commentary article and a review article were published.

We focused on the original articles of these three clinical medical journals published for the first time in the medical literature and presenting novel findings. Their continued validity and relevance were established by at least one citation in the articles of PubMed central journals published during the present decade (2010 to 2018) (CT_9). The themes of all cited articles had to be closely related to those of the present decade's articles, otherwise they were excluded from the selection strategy. The number of citations over half-hundred years (1967–2018) was noted CT_{50}). The study was performed during 2017–2018.

Results

Over the one-year period (1966), 525 articles were published in the NEJM (volumes 274 and 275). Of these, 298 were original articles, consisting of 163 observational studies, 18 clinical trials and 117 case reports. All the clinical trials were open and controlled, but none were randomized, and they had small sample sizes. Among the 299 articles (comprising 298 original articles plus one article under the category of "Medical Intelligence"), the following 12 articles were evaluated as being both valid and relevant half-hundred years after publication.

1 "Some re-evaluations of the build and blood pressure study, 1959 as related to ponderal index, somatotype and mortality"[1] examined the relationship between mortality rate and body volume. The weight and height of a sample of approximately 350 000 people insured by the US Society of Actuaries were used and the ponderal index (height in inches divided by the cube root of weight in pounds) was calculated as a measure of body volume. They found that mortality rate increased in an exponential manner as the index decreased from 15 (the thinnest individual) to 11 (the thickest individual) ($CT_9=3$, $CT_{50}=23$).

2 "Arterial changes in the lungs in cirrhosis of the liver–lung spider nevi"[2]: Finger clubbing and cutaneous spider nevi associated with cyanosis are signs of increased shunting between peripheral arteries and veins in patients with advanced cirrhosis, whose arteries have unsaturated oxygen. On postmortem examination of the lungs of 13 patients with advanced cirrhosis, excessive arteriovenous shunts were found in the alveolar walls of all patients. The dilated precapillary shunts were observed using intra-arterial injection of a gelatin suspension. Total vessels to the alveoli were increased in those with cirrhosis compared to the six controls ($CT_9=16$, $CT_{50}=50$).

3. "Radiation-related leukemia in Hiroshima and Nagasaki, 1946–1964. I. Distribution, incidence and appearance time"[3]: In cooperation with the Japanese National Institute of Health, research institutes in the USA studied the effects of exposure to radiation from the atomic bombs dropped on Hiroshima and Nagasaki. The occurrence of acute and chronic leukemia in survivors in two areas near the hypocenter was assessed in 5-year periods (1945–1949, 1950–1954, 1955–1959 and 1960–1964).[3] In areas <1500 m from the hypocenter, leukemia developed in 6.22, 48.12, 36.74 and 14.78 per 100 000 individuals, respectively. In areas 1500–10 000 m from the hypocenter, the corresponding rates were 1.24, 1.98, 4.15, and 2.2 individuals per 100,000. Acute leukemia particularly occurred in the first five years after exposure. In 1950–1954, the rates of leukemia in areas <1500 m from the hypocenter were excessive in comparison to those in areas 1500–10 000 m from the hypocenter. The population aged <30 years tended to develop acute leukemia in the areas <1500 m from the hypocenter rather than 1500–10 000 m from the hypocenter ($CT_9=4$, $CT_{50}=8$).

4. "Predictive value of a single diagnostic test in unselected populations"[4]: A statistics paper addressed the importance of defining the "predictive value" of a positive diagnostic test. When the sensitivity and specificity of a diagnostic test are known, we are unable to predict the importance of the results when the prevalence of a disease in a population is very variable. Given a test with 95% sensitivity and specificity, when the prevalence of a disease is very low (about 1%), we would have a low chance of distinguishing diseased and non-diseased individuals; the probability is about 16.1%. When the prevalence of a disease is 50%, the chance of distinguishing the diseased and non-diseased individuals increases considerably, with 95% reliability ($CT_9=19$, $CT_{50}=102$).

5. "Thyroid nodules as a late sequela of radioactive fallout in a Marshall Island population exposed in 1954"[5]: In 1954, the small population of the Marshall Islands were accidentally exposed to radioactive fallout involving radioiodine due to the detonation of a thermonuclear device. They were exposed for two days before they were evacuated and lived until 1957 on another island. The calculated exposure dose over the two

days was 175 Rads of gamma radiation. Thyroid nodules developed in 11 of the 82 exposed people, and one of the 11 developed carcinoma. In contrast, only 1 in 200 native people in the same region who were not exposed to radiation developed thyroid nodules. Among the children, 55% who were exposed developed thyroid abnormalities ($CT_9=3$, $CT_{50}=8$).

6. "A glucagon-secreting alpha-cell carcinoma of the pancreas"[6]: A glucagon-secreting pancreatic islet cell tumor with symptoms including eczematous dermatitis of the upper and lower extremities, diabetes, and liver metastases was reported for the first time ($CT_9=6$, $CT_{50}=26$).

7. "Treatment of bone-marrow failure by isogeneic marrow infusion"[7]: Bone marrow transplantation was successfully carried out in an 18-year-old boy with aplastic anemia; the donor was his identical twin. The procedure was carried out by the main study author, who had used this new approach for another patient two years earlier. An analysis of the 10 reported cases of bone marrow transplantation involving identical twins over six years prior to this publication revealed a 50% survival rate. It was concluded that such patients should be treated promptly using stem cells from their healthy identical twins ($CT_9=2$, $CT_{50}=4$).[8]

8. "Pneumonia due to *Mycoplasma pneumoniae*. Its incidence in the membership of a co-operative medical group"[9]: The epidemiology of the occurrence of all types of symptomatic pneumonia (and especially that caused by *Mycoplasma pneumoniae*) was studied in a small community of 72,992 people during 1964. The pneumonia diagnoses were verified clinically by physicians and by X-ray. Overall, in all age groups, the incidence rate was 12.9 per 1000 years. The incidence rate of pneumonia associated with Mycoplasma (as diagnosed by throat swab cultures and serology) was 0.9 per 1000 years. While the incidence of pneumonia generally peaked in the very young age group (aged <9 years), Mycoplasma-related pneumonia appeared in all age groups and it had a mild clinical course ($CT_9=2$, $CT_{50}=16$).

9. "Relief of angina pectoris by Valsalva maneuver" in the "Medical Intelligence" category[10]: The effect of using the Valsalva maneuver on angina pectoris was observed with prompt relief in six patients. This effect has since been evaluated in 24 patients with ischemic heart disease, and it was found in 18 of them ($CT_9=1$, $CT_{50}=2$).[11]

10. "Gonadotropin-producing anaplastic large-cell carcinomas of the lung"[12]: Gynecomastia was found in four patients with anaplastic large-cell bronchial carcinoma due to the production of gonadotropin in neoplastic lung tissue. Depletion of hormone activity in the pituitary gland was observed in three of the patients and increased urinary excretion of gonadotropin was observed in all four. The endocrine nature of gynecomastia and its nature as a paraneoplastic symptom of carcinoma was emphasized ($CT_9=2$, $CT_{50}=20$).

11. "Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula"[13]: Reliable and stable access to blood vessels in patients with renal failure was essential for continuous establishment of chronic hemodialysis and patient longevity. Quinton's development of an anastomosis technique involving connecting an artery and a vein via an exterior Teflon shunt in 1961 was the first step in this direction. However, this external shunt had no stability and only had short-term usefulness (up to a few months). The introduction of a subcutaneously-prepared fistula between the radial artery and vein has remained an easy and successful dialysis method up until the present time, even for use at home ($CT_9=44$, $CT_{50}=107$).[14,15]

12. "Twelve-year follow-up of New York narcotic addicts. II. The natural history of a chronic disease"[16]: A 12-year follow-up study of 50 male narcotic addicts revealed that unemployment prior to the start of narcotic abuse was the most important factor for continuing narcotic abuse. Parental loss during childhood was another factor.

These 12 articles represent 4% (12/299) of all original articles published in NEJM in 1966 ($CT_9=2$, $CT_{50}=7$).

In Lancet, in 1966, among all 716 categories, 628 original articles were published in two volumes consisting of 390 observational, 29 diagnostic, 82 therapeutic, 61 case reports, 38 animal experimental, and 28 *in vitro* studies. Among the 82 therapeutic trials, 30 were randomized, controlled and mostly double-blind. Among all articles, the following 11 were identified as still being relevant and valid:

1. "Treatment of chronic portal-systemic encephalopathy with lactulose"[17]. Lactulose is a disaccharide which is not hydrolyzed during its passage through the small intestine into the colon, where it is split by bacteria into organic acids, inducing osmogenic diarrhea and decreasing fecal pH. Both effects appear to reduce the production of toxic nitrogenous substances from proteins. The effect of lactulose on the improvement of encephalopathy was compared with the administration of neomycin and restricted protein in two patients with advanced liver cirrhosis ($CT_9=12$, $CT_{50}=38$).

2. "Monosaccharide malabsorption in young infants"[18]. Four babies developed severe diarrhea after birth. No monosaccharides, glucose, galactose, and fructose could

be absorbed. Biopsies from small intestinal mucosa were histologically normal and contained normal levels of activity of all disaccharidases. The most satisfying diet contained 2.5% casein, 3%–4% butterfat, 25 mg deoxycholate per 100 mL as emulsifying agent and large amount. Persistent hyperchloremic acidosis was present in all children. No evidence of genetic defect was found. The disorder remained temporary over two to five months. A return to cow milk and mixed feeding was successful in all children who subsequently developed normally (CT_9=5, CT_{50}=65).

3 "Effect of lymphoid cells from the lymph of specifically immunised sheep on the growth of primary sarcomata in rats"[19]. 3:4-benzpyrene can induce the occurrence of fibrosarcomata in rats. When lymphocytes from the lymph nodes of a sheep, which was immunized with antigens of this tumor were injected in the rats, the growth of the chemically induced tumor could be retarded. The action of the heterologous lymphocytes was specific to the particular tumor for immunization (CT_9=8, CT_{50}=83).

4. "Measurement of rate of gastric emptying using chromium-51"[20]. Radioactive sodium chromate (51-Cr) was put into a breakfast consisting of porridge with eggs. The emptying rate of the stomach was measured by scanning the radioactivity in the stomach area. Emptying occurred in an exponential manner (CT_9= 8, CT_{50}= 33).

5. "Fatal granulomatous disease of childhood, an inborn abnormality of phagocytic function"[21]. Leucocytes from the boys studied *in vitro* were not capable to kill and digest phagocytized bacteria, which occurred sooner compared to control subjects. Abnormality of cell function and lack of lysosomal and bactericidal reduction enzymes might facilitate the development of granulomatous disease (CT_9= 11, CT_{50}=57).

6. "Jejunal bacteriology and bile-salt metabolism in patients with intestinal malabsorption"[22]. In jejunal fluid of patients with stagnant loop syndrome and patients with partial gastrectomy, free bile acids and the number of bacteria were measured. Patients with numbers higher than 100×10^6 bacteria in the fluid had all free bile acids, especially deoxycholic acid in toxic concentration and pronounced steatorrhea and those with bacterial count less than 40×10^6 per mL had free bile acids and less steatorrhea. Treatment with antibiotics in patients with stagnant loop syndrome reduced the bacterial counts and resulted in disappearance of free bile acids and the reduction of the degree of steatorrhea. These observations suggest that bacterial activity in small intestine is responsible for altered bile salt metabolism and the appearance of steatorrhea in patients with stagnant-loop syndrome (CT_9=2, CT_{50}=33).

7. "Serum-free-fatty-acids after acute myocardial infarction and cerebral vascular occlusion"[23]. Serum free-fatty-acids (FFAs) were studied in patients with acute myocardial infarction, acute cerebral vascular occlusion, or acute coronary insufficiency. During the first twelve to twenty-four hours after acute myocardial infarction and acute cerebral vascular occlusion, a striking increase of serum FFA occurred, which gradually decreased during the subsequent forty-eight hours towards normal levels. There was a less striking increase of serum-FFA levels in patients with acute coronary insufficiency and these levels fell rapidly reaching normal limits within twenty-four hours. It is suggested that the release of catecholamine by severe anoxia mobilizes FFA from adipose tissue (CT_9=4, CT_{50}=21).

8 "Experimental autoimmune thymitis. An animal model of human myasthenia gravis"[24]. When guinea pigs were immunized with either thymus or muscle, a myasthenic neuromuscular block occurred by electromyographic testing. Thymectomy prevents the occurrence of the neuromuscular block. In the thymus of immunized animals, collections of lymphocytes appeared in the thymic medulla. These experiments suggest the presence of an autoimmune reaction in the characteristic neuromuscular block of myasthenia gravis (CT_9=1, CT_{50}=29).

9. "Hashimoto's disease and encephalopathy"[25]. Some months after the apparent onset of Hashimoto's disease in a 48-year-old man, within few weeks hemiplegia, hemiparesis, monocular blindness, confusion, and agitation as symptoms of encephalopathy appeared with alternating improvement lasting over a year. In the end, recovery was spontaneous and complete (CT_9=54, CT_{50}=65).

10. "Hyperacute rejection of kidney allografts, associated with pre-existing humoral antibodies against donor cells"[26]. Two women in terminal uremia received cadaver kidney transplantation. Urine secretion after transplantation appeared normal over 2 minutes but gradually decreased after 10 minutes and ceased after one hour. By continuation of hemodialysis, the cadaver kidneys were removed a few days after transplantation. Both women died two and three months later. Both patients were heavily isoimmunized by blood transfusions, and before the transplantations, their serum contained leucocyte agglutinins, complement-fixing thrombocyte and kidney antibodies. The antibodies in the sera of both patients were active against antigens from the cadaver donors. It is suggested that these humoral antibodies played an important role for the hyperacute rejections (CT_9=29, CT_{50}=108).

11. "Metronidazole in amoebic dysentery and amoebic liver abscess[27]: Eleven patients with amoebic abscess and 56 patients with amoebic dysentery were successfully cured with intake of 3 × 800 mg metronidazole daily for 10 days with no significant side effects (CT_9=2, CT_{50}=16).

These 11 selected publications represent 1.75% (11/628) of all original articles in LANCET in 1966.

In two volumes of DMW in 1966, 282 articles were published, of which 221 were original articles consisting of 77 observational, 39 therapeutic, 28 diagnostic, 57 case reports, 7 animal, 4 *in vitro*, and 9 other studies. Among 39 therapeutic studies, there were 9 non-randomized, non-blind but controlled studies. Among all original articles, one was relevant:

12. "On the thrombolytic therapy of recent myocardial infarction. 2. Results of electrocardiographic studies[28]. In one multicenter study in cooperation with clinics in Switzerland, 297 patients with acute heart infarction were treated initially over 15 hours with streptokinase, then with an anticoagulant phenprocoumon compared with another group of 261 infarct patients with the anticoagulant alone. In both groups, heparin was given in optimal dose on the first days to achieve the therapeutic fibrinolytic effect of anticoagulant. The decrease of infarct-induced ST-segment elevation in electrocardiogram appeared in 50% of cases in the Streptokinase group on the second day after therapy, while this occurred on the 20th day in the comparison group. The 40-day mortality rate of patients in the streptokinase group was 14.1% less than the other group with 21.7% ($P < 0.05$).[29] The favorable effect of streptokinase was proven for the first time in a study with 22 patients in 1959. However, this study was uncontrolled[30] (CT_9=1, CT_{50}=2). The proportion of important publications in DMW 1966 corresponds to 0.45% of all original articles (1/221).

Discussion

Science and medicine are progressive and thus, it is no wonder that the relevance of most publications in these three important journals diminished over five decades. All three journals were scientifically the most renowned in the clinical medicine in their country at that time. All had been established more than one hundred and fifty years ago. The percentage of papers that are currently relevant after 50 years (4% in NEJM and 1.75% in LANCET) seems remarkable. The low citation rate of publications in the German DMW is in part due to the fact that the second world war (WWII) destroyed all scientific institutions in Germany and many important scientists emigrated before, during and after the war. All scientific articles in DMW, including the abstracts, were written only in German. After WWII the primary language of science changed from German to English which limited audience to German-speaking scientists. Recent observations have shown that English has become the language of publication of the most important papers from all countries, however this may change to another language such as Chinese.

The introduction of predictive value in statistical analysis, the knowledge of high mortality of obese subjects, the application of new therapies like lactulose in hepatic encephalopathy, metronidazole in amoebic diseases, antibiotics in bacterial-induced malabsorption, arteriovenous fistula for hemodialysis in patients, bone marrow transplantation in oncology and discoveries in the causes of some diseases all represent enormous progress made in clinical medicine emerging from publications in 1966, all of which had enormous influences on the medical sciences today. It should not be surprising that many papers were "lost" in that much that is science consists of incremental knowledge some of which is confirmatory, some moving toward a dead end, and some providing new insights and directions. Most of the papers published in these three general clinical journals in 1966 that are still currently relevant provided new insights, directions, or therapies and served as foundation articles. In the last two decades, the impact factor of a scientific journal has become a major criterion signifying the importance and novelty of the articles published in that journal. This standard of judgment is related to the number of citations over a limited time period and makes it difficult to separate topical from important. In conclusion, it is proposed that half hundred years impact index can be used as an example of measuring long-term sustaining quality of a journal in addition to impact factor, under the condition that the journal exists for more than half-hundred years. For a better judgment, focusing on the number of citations in the last 10 years is recommended.

Conflict of Interest Disclosures

None.

Ethical Statement

Not applicable.

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