Vitamin A as "Anti-Infective" Therapy, 1920–1940[1]

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ABSTRACT In the last fifteen years, a large series of controlled clinical trials showed that vitamin A supplementation reduces morbidity and mortality of children in developing countries. It is less well known that vitamin A underwent two decades of intense clinical investigation prior to World War II. In the 1920s, a theory emerged that vitamin A could be used in "anti-infective" therapy. This idea, largely championed by Edward Mellanby, led to a series of at least 30 trials to determine whether vitamin A—usually supplied in the form of cod-liver oil—could reduce the morbidity and mortality of respiratory disease, measles, puerperal sepsis, and other infections. The early studies generally lacked such innovations known to the modern controlled clinical trial such as randomization, masking, sample size and power calculations, and placebo controls. Results of the early trials were mixed, but the pharmaceutical industry emphasized the positive results in their advertising to the public. With the advent of the sulfa antibiotics for treatment of infections, scientific interest in vitamin A as "anti-infective" therapy waned. Recent controlled clinical trials of vitamin A from the last 15 y follow a tradition of investigation that began largely in the 1920s. J. Nutr. 129: 783–791, 1999.

KEY WORDS: • *vitamin A* • *anti-infective therapy* • *morbidity* • *mortality* • *immunity*

Vitamin A supplementation is an important public health intervention to reduce mortality from infections among children in developing countries. In the 1980s and early 1990s, several large randomized, double-blind, placebo-controlled clinical trials were conducted in developing countries around the world, and these studies showed that vitamin A supplementation could reduce child mortality by about one-third (Beaton et al. 1993). Improving the vitamin A status of children through vitamin A supplementation is one of the most cost-effective health interventions known (World Bank 1993). High-dose vitamin A is now recommended therapy for measles in many developing countries and for selected circumstances in developed countries (World Health Organization 1987, American Academy of Pediatrics 1993). Although vitamin A has been undergoing investigation in clinical trials in the last two decades, these recent trials are largely a continuation of clinical investigation that began in the 1920s.

Prior to World War II, there was great interest and debate surrounding the use of vitamin A as "anti-infective" therapy. An idea was conceived that vitamin A could strengthen the immune system and would help fight infections. A series of at least 30 studies was conducted to evaluate vitamin A as a means of reducing infections and mortality. The early clinical investigations of vitamin A had some spectacular successes and notable failures. The public seized upon the use of vitamin A as "anti-infective" therapy, but the value of vitamin A in reducing morbidity and mortality from infections was not more widely recognized until 50 y later. This paper will examine the rise of the idea of using vitamin A as "anti-infective" therapy and the evaluation of this theory through clinical trials from 1920 to 1940.

THE INFANT WELFARE MOVEMENT

In 1910, the first annual meeting of the American Association for the Study and Prevention of Infant Mortality was held at Johns Hopkins University. The association was founded out of concern over the belief that one of every four infants died before 12 mo of age in the United States. Out of a total infant population of 1.5 million, an estimated 300,000 deaths occurred each year under 12 mo of age (Knox 1910). The association had broad membership that included social workers, public health officials, and philanthropists, and its founders included William Henry Welch from Johns Hopkins, the pediatrician L. Emmett Holt, and the nutritionist Alfred Hess. The immediate goal of the society was to reduce infant mortality by half, and many members of the association attributed such excessive mortality to parental ignorance and indifference. The strategies being considered to combat infant mortality were diverse, and its members pointed out the need for more accurate vital statistics, the importance of maternal nursing and the need to educate mothers. The association did not restrict its activities to the realm of academia, as they had travelling exhibits and also sent their reports to popular women's magazines at the time. Magazines such as *The Pictorial Review* and *Ladies Home Journal* were quick to pick up the crusade of the association with advice columns aimed at mothers and occasional lay articles written by members of the association.

The movement in the United States was part of a larger

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international infant welfare movement that began in Great Britain. The major causes of infant mortality at the time were epidemics of diarrhea among infants during the summer, also known as the "summer complaint" and acute upper and lower respiratory disease, known as the "winter complaint." Arthur Newsholme, George Newman, and other architects of public health reform in Great Britain thought that fecal contamination of food and milk were responsible for epidemics of summer diarrhea. George Newman was medical officer of health for Finsbury, one of the poorest and most crowded metropolitan boroughs in Bedfordshire. He made careful observations of infant mortality and pointed out that epidemic diarrhea among infants was steadily increasing, especially in towns "where the lamp of social life burns low." Newman (1906) argued that the health of community should be gauged by the infant mortality rate rather than the general death rate. Thus, he considered it a sign of social degeneration that Great Britain should have a falling overall death rate but little change in the infant mortality rate over the preceding 50 yr.

In the late nineteenth century, sporadic efforts were being made to improve the urban milk supply in large cities (Meckel 1990). Newman pointed out that breastfed infants suffered less from summer diarrhea than infants who were fed artificial formula or cow's milk. He considered the high infant mortality rate to be mainly a problem of motherhood, and he emphasized proper training of mothers and promotion of breastfeeding. Pasteurization of milk and milk stations were other measures that were proposed to reduce infant mortality rates. It took a long time for milk to be transported from the farm to the city, and bacterial contamination of cow's milk was common, especially during the hot summer days. Milk was an especially good medium for bacterial growth. In addition, infants were fed using what pediatrician Robert Hutchinson (1940) termed "foul, sour-smelling contraptions" known as tube bottles.

The American Association for the Study and Prevention of Infant Mortality was founded at a time when improvement of the urban milk supply was having no apparent effect upon infant mortality rates (Meckel 1990). L. Emmett Holt (1910) declared that infant mortality would not be solved simply by purifying milk and by establishing milk stations. Milk stations may have had little influence since they only reached a very small proportion of urban infants. In his time, Holt (1900a) was perhaps the best known and influential pediatrician in the United States, author of the widely read book, *The Care and Feeding of Children*. Holt considered nutrition to be the most important branch of pediatrics and declared that, "The largest part of the immense mortality of the first year is traceable directly to disorders of nutrition" (Holt 1900b). The nutritional measures that could be taken to save children at the time were part of an evolving debate.

Emergence of the vitamins. The nutritional theories of the German chemist Justus von Liebig (1803–1873) dominated scientific discussion for many years and were also echoed in lay publications. In *The Pictorial Review*, Anna Steese Richardson (1916) gave popular advice on motherhood, nutrition, breast-feeding, and other health-related issues in a regular column. Her dietary advice to expectant mothers summarizes Liebig's doctrine: "Stoke the engine of your body with the right sort of coal, keep it clear of cinders and clinkers, cleanse it with pure water, renew the worn parts with rest . . . What is the right kind of coal? Food-stuffs classified according to their chemical properties . . . water, mineral matter, proteins, carbohydrates, and fats." Liebig held that dietary proteins are almost directly unchanged in building up the protein in tissues, and that carbohydrate and fat merely provided fuel to be burned with oxygen from the lungs, thus providing heat. The likening of the human body to a steam locomotive was a popular simplification that was often used by Liebig's successors.

The laboratory provided well-controlled conditions for the critical examination of nutritional theories through the administration of experimental diets in animals. Over a 25-yr period, several investigators made similar observations in different institutions that suggested the existence of vitamin A (Steenbock 1932, Wolf and Carpenter 1997). Two students who worked in the laboratory of Gustav von Bunge at the University of Dorpat challenged Liebig's theory regarding the essential food components. Nicholai Lunin (1881) determined that mice cannot survive on a purified diet of fats, carbohydrates, proteins, and salts alone; however, he noted that mice could survive when milk was added. Lunin concluded "other substances indispensable for nutrition must be present in milk besides casein, fat, lactose, and salts." His idea received considerable dissemination in von Bunge's (1887) widely-read Lehrbuch der physiologischen und pathologischen Chemie. Ten years later, another student, C. A. Socin (1891), performed experiments with simplified diets in mice and found that there was an unknown substance in egg yolk which was essential for life. At the University of Utrecht, Cornelius Pekelharing (1905), showed that mice are able to survive on diets in which small quantities of milk are added, and Wilhelm Stepp (1911) showed that if the milk supplied to mice was extracted with alcohol-ether (thus removing the fat-soluble substance later known as vitamin A), the mice could not survive.

Other experiments with animals suggested that there were other unknown substances in food that were necessary to support health. In 1886, C. Eijkman was sent to the Dutch East Indies to work on the problem of beriberi. He demonstrated that chickens raised on polished rice alone developed a paralytic disorder similar to human beriberi, and that this disorder could be corrected by a diet of unpolished rice, and it was soon demonstrated that the bran portion of rice contained a substance that could prevent beriberi. Scurvy was produced in guinea pigs on experimental diets, and these animals were cured with fresh fruits and vegetables (Holst and Frölich 1907). Frederick Gowland Hopkins (1906) at Cambridge University expressed the belief that there were "unsuspected dietetic factors" besides proteins, carbohydrates, fats, and minerals that were vital for health, especially in rickets and scurvy.

Much of the early work with experimental diets in animals in the United States was conducted by Thomas Osborne and Lafayette Mendel (1911, 1913) at Yale University, and their work suggested that a fat-soluble substance in butterfat was needed to support the growth of rats. After a period of illness, Hopkins published work he undertook in 1906–1907 which, similar to the findings of Pekelharing, showed that mice could not survive on a purified diet without milk. Hopkins (1912) postulated the existence of what he called "accessory factors" in foods that were necessary for life. Casimir Funk (1912) named these substances "vital amines" or "vitamines" over the belief that these accessory factors were chemical amines, similar to thiamin, the vitamin involved in the deficiency disorder, beriberi. Elmer McCollum and Marguerite Davis (1913) at the University of Wisconsin confirmed that this accessory factor was found in butter, and they dubbed it "fat-soluble A." Soon the term "fat-soluble A" was combined with Funk's designation to become "vitamine A."

These early animal studies were criticized because it was thought that under caged conditions, the purified diets given to animals were too monotonous and distasteful so that the

animals allowed themselves to starve to death, or that the chemical processing to purify the foods had a deleterious effect that led to intoxications or rendered the food unsuitable for nutrition (Nicholls 1938). Often the vitamin A-deficient animals developed ocular abnormalities, including dryness of the eyes, ulceration of the cornea, and blindness. Many clinicians were skeptical that the findings from animal experiments could be extrapolated to humans, given the severity of nutritional deprivation (Cramer 1924).

Clinical observations in children. Prior to the period in which Hopkins and others were observing that milk or butter contained an unknown factor that was essential to life in animals, similar clinical observations were made among humans. Numerous descriptions exist of blinding eye lesions and high mortality throughout the eighteenth and nineteenth centuries. Many of these observations came from homes for foundling children, usually among infants who were not breastfed (Billard 1828, Brown 1827, Ratier 1824). More detailed descriptions were made in the early twentieth century (Wolf 1998). Masamichi Mori (1904) described nightblindness, cornea ulcers, blindness, and high mortality among children during summer epidemics of diarrhea in rural Japan. The condition was locally known as "hikan." Mori attributed the problem to lack of fat in the diet, and he noted that milk, cheese, butter, and bacon were not common in the Japanese diet.

Adalbert Czerny and Arthur Keller (1906) noted a nutritional problem in children in Breslau which they called "Mehlnährschaden." The exact translation is elusive, but it literally means "flour-based nutritional disturbance." Mehlnährschaden was described as a cessation of weight gain, emaciation, ocular abnormalities, and depressed immunity, and the condition was noted in children who received flour-based preparations as a substitute for milk or breastmilk. The recommended treatment for Mehlnährschaden was breastfeeding. Further descriptions of xerophthalmia (the typical eye lesions of vitamin A deficiency), diarrhea, and high mortality were made among poor children in the east end of London (Stephenson 1910) and among children in Denmark who were raised on skim milk (Bloch 1919). Sporadic case reports of blinding xerophthalmia continued through the 1920s at places such as Johns Hopkins Hospital and Infant's Hospital in Boston among children who were fed condensed milk lacking in vitamin A (Ross 1921, Wilson and DuBois 1923).

Although these clinical descriptions were dramatic, others argued that these cases were only extreme examples, and on the whole, vitamin A deficiency was rare in Great Britain, Europe and the United States. But in an address published in *The Lancet*, William Cramer (1924) expressed belief that subclinical vitamin A deficiency might actually be common, a condition he called "the borderline between health and disease." He noted, "These effects [from lack of vitamins] are so little obvious that they have up to now been overlooked." Cramer surmised that children in this borderline state would appear well but under stress of infection would do poorly because of an underlying inadequate intake of vitamins. The discovery of the vitamins, Cramer noted, "has placed in our hands a therapeutic and prophylactic weapon of quite unsuspected possibilities in improving the health of the community." Further evidence for a relationship between infection and vitamin A deficiency was soon to come from the animal laboratory.

VITAMIN A AS THE "ANTI-INFECTIVE" VITAMIN

One day in 1925, Edward Mellanby, a Professor of Pharmacology at the University of Sheffield, was summoned to his animal laboratory because some of his dogs were dying. Mellanby had previously received a research studentship to work under the guidance of Frederick Hopkins, and Mellanby was extending the research of his mentor on vitamin A. He was raising a large colony of dogs, and about two-thirds of them had been experimentally rendered vitamin A-deficient. An epidemic of bronchopneumonia was sweeping through the colony, and this accident allowed for a fortuitous observation. On post-mortem examination of 330 dogs, Mellanby (1926) noted that the bronchopneumonia was largely restricted to the vitamin A-deficient dogs. He speculated that the observations of the increased susceptibility to respiratory infections might have possible relevance to children with respiratory illness.

Mellanby and Harry N. Green, another physician at Sheffield, continued to investigate the idea that vitamin A could be necessary for immunity to infections (Green and Mellanby 1928). They described increased infections in vitamin A-deficient rats, and this led them to dub vitamin A an "anti-infective agent." Specifically, they noted that deficiency of vitamin A, but not vitamin D, caused increased infections in the animals. Vitamin A deficiency appeared to produce a breakdown in mucosal surfaces in the lungs and elsewhere, allowing infections to occur. They theorized: "On the basis of these facts we suggested that vitamin A plays a significant part in raising the bodily resistance to infection." By calling vitamin A the "anti-infective" vitamin, Green and Mellanby had made the most explicit statement of such a theory and laid down a challenge to scientific investigators. Different measures were being evaluated for reducing mortality among infants and young children, and their theory underwent an intensive phase of investigation through clinical investigations of vitamin A (Lancet 1931).

The Home for Hebrew Infants. The Home for Hebrew Infants in New York, an asylum run by Dr. Alfred Hess and caring for over 400 children, provides an example of what was being done in general to improve infant health during this period. Due to death or destitution, many parents left their infants to the care of the city, and the Home for Hebrew Infants was considered one of the better institutions in New York. Hess was appalled by the mortality rates in the institutions housing infants in large American cities. In one large infant asylum in New York City, 50% of children died before reaching 24 mo of age, and in another, one third of infants died before their second month under institutional care. Hess (1916) warned that this neglect did not occur in all institutions caring for infants, noting that the infant mortality rate in his institute was only 16% in 1915. He attributed this "low" mortality rate to a minimal 9 mo of training nurses, a ratio of one nurse to five infants during the day, and a milk laboratory.

By the late 1920s the major causes of mortality changed among infants and young children in Europe, Great Britain and the United States. The epidemics of summer diarrhea and high infant mortality had virtually disappeared to the point that epidemic diarrhea was declared defeated in Great Britain by the early 1930s (Lancet 1934). New emphasis was being placed upon the "winter complaint," which was now the leading cause of death. But statistics from the Home for Hebrew Infants show that the case fatality rates for pneumonia were also dropping during the same period. The case fatality rate for pneumonia had dropped by nearly two-thirds, from 23% in a period from 1916 to 1922 to about 7% from 1923 to

1927 (Barenberg et al. 1929). Hess's colleagues attributed these changes in diarrheal and respiratory disease to model institutional care, which included unobstructed, sunny infirmaries, large verandas and avoidance of overcrowding or "hospitalism."

The physicians at the Home for Hebrew Infants thought that further interventions could be made to reduce the incidence of respiratory disease, and in 1925 they conducted a study of ultraviolet radiation, or heliotherapy, from a mercury vapor lamp to reduce respiratory infections. Forty infants in two wards were divided into "irradiated" and "nonirradiated" groups. Final analysis revealed that irradiation appeared to have no effect on the incidence of respiratory disease during the winter (Barenberg et al. 1926). The investigators thought heliotherapy failed because they were using the wrong type of lamp, and the following year they repeated a similar study using a carbon arc lamp. Again they noted no impact of ultraviolet radiation upon the incidence of respiratory infections among the 19 infants in the clinical trial (Barenberg and Lewis 1928). Disappointed with these results, another trial was conducted in 1928 to determine if "aseptic nursing" could reduce the incidence of respiratory disease. The two main infant wards of the home were divided into intervention and control wards. The intervention included hand scrubbing with mercuric chloride, use of surgical masks by all nurses, physicians, and attendants, prohibition of physical contact with infants, and boiling of all plates, spoons, and cooking utensils used by the infants. Among the 79 infants in this trial, "aseptic nursing" appeared to have little impact upon the incidence of respiratory disease (Abramson and Barenberg 1929).

During the time that heliotherapy and aseptic nursing were being tested, malnutrition was virtually unknown in the Home for Hebrew Infants. Alfred Hess, a pioneer in research on vitamins C and D, ensured that all children under 3 yr of age received liberal amounts of orange juice and cod-liver oil daily. Hess was concerned that respiratory disease continued to thwart all preventive efforts, and he was intrigued by Mellanby's proposal to use vitamin A as "anti-infective" therapy. A study was conducted in which all infants in the study received at least what is now considered to be the recommended dietary allowance of vitamin A, and the treatment groups received additional vitamin A in the form of cod-liver oil. Additional cod-liver oil had no effect upon respiratory infections (Barenberg and Lewis 1932). Hess thought that perhaps they were not given enough vitamin A, and another study was performed in which even higher doses of vitamin A were used, to no avail (Hess et al. 1933). All infants in their studies received vegetables, eggs and butter, which are foods rich in vitamin A. Hess concluded that young children do not require more than the vitamin A contained in 750 mL of milk per day, and that giving thousands of units of vitamin A "constitutes therapeutic absurdity, which, happily, will prove to be only a passing fad."

Vitamin A and the common cold. Other studies were conducted to determine if vitamin A could prevent the common cold in school children. One such trial, conducted in the Long Beach, New York, public schools in 1932, included a control group not taking vitamin A, but enthusiasm was so high that parents in the control group started giving their children vitamin A at home. The investigators concluded: "Because of the difficulty in controlling the outside factors of a demonstration of this kind, it is impossible to make an unqualified statement as to the efficiency of vitamin A in cold prevention" (Tress 1935). Physicians at the Montreal Foundling and Baby Hospital, like their colleagues at the Hebrew Home for Infants, had evaluated vaccine, ultraviolet ray, and cod-liver oil, but they considered their results were "so uniformly unsuccessful that it has not been thought worthwhile to make any publication" (Wright et al. 1931). Their trial of regular vs. high doses of vitamin A showed that vitamin A in excessive amounts does not protect infants against the common cold.

Medical and nursing students were recruited into a study conducted at the Case Western Reserve University in 1933 (Shibley and Spies 1934). Vitamin A was given in the form of halibut liver oil to more than 200 volunteers, and the students filled out a card that documented any respiratory symptoms each week. The investigators used random sampling to assign volunteers to treatment groups, and they also attempted to conceal their treatment allocation by giving all participants tomato juice, with or without halibut liver oil. The investigators concluded that vitamin A had no effect on either the incidence or severity of colds, but noted that there was a reduction in the duration of colds in the vitamin A-treated group. For data analysis, the investigators mention that they took the data to a doctor in their Department of Hygiene and Bacteriology, and he reported that the results "were significant statistically." Few studies of this period included a statistical analysis, and it was usually mentioned in a footnote.

By 1940, there had been at least 16 studies involving a total of over 9000 subjects to determine if vitamin A, mostly in the form of cod-liver oil, could reduce the incidence of respiratory infections **(Table 1).** These investigations were conducted in places such as Malmö, Peterhead, New York, and Chicago, and the majority were conducted in the United States. The classroom or Infant Home were the primary sites for conducting the clinical trials. Overall, the results were mixed, with about half of the studies showing an impact of vitamin A on respiratory infections, and the others showing no effect. As suggested by Hess et al. (1933), no therapeutic benefit of vitamin A was noted for infants who were already sufficient in vitamin A. Other studies showed that vitamin A showed promise as a specific treatment for infections such as tuberculosis and typhoid fever and as a means of preventing skin infections in children **(Table 2).** After Edward Mellanby visited Johannesburg in 1929, his enthusiasm about vitamin A convinced local investigators to conduct a trial of vitamin A as therapy for pneumonia among mine laborers at the Crown Mines (Donaldson and Tasker 1930). Their results showed that vitamin A reduced mortality, but a subsequent study at the Rand Mines in Johannesburg was unable to confirm these findings (Orenstein 1932). May Mellanby, the wife of Edward Mellanby and a fellow student from Cambridge, also conducted a series of studies in Sheffield and Birmingham that suggested that cod-liver oil could reduce the incidence of dental caries in children (Mellanby et al. 1924), but these findings were not confirmed in a subsequent study (Day and Sedwick 1934).

Industrial absenteeism. A great effort was made to use vitamins to reduce industrial absenteeism by both adults and children. In Chicago, Katharine Rich (1920) noted that more and more children were joining the labor force because of the increased cost of living. She was interested in improving the nutritional status of these children so that they could be healthier child laborers and would not drop out. Because of malnutrition, Rich noted that children "lost their jobs, became discouraged and gravitated into becoming rolling stones, thus easily falling prey to vicious and criminal companions." In the following years she conducted investigations and made recommendations aimed at improving the nutrition of children in the Chicago schools.

In the United States, a major concern among industry in the 1930s was the loss of productivity due to illness in the labor force of 36 million. It was estimated that 250 million

TABLE 1

Studies of vitamin A as "anti-infective" prophylactic therapy, 1920–1940

Subjects	*n*	Location	Intervention	Therapeutic effect of vitamin A	Reference
Prevention of respiratory infections					
Children	1721	Malmö	Cod-liver oil vs control	↓ Incidence of disease	Widmark and Svensson (1928)
Infants	60	Montreal	Vitamin A vs. control	No effect on incidence of disease	Wright et al. (1931)
Infants	188	New York	Small vs. moderate vs. high intake vitamin A	No effect on incidence of disease	Barenberg and Lewis (1932)
Adults	313	United States	Cod-liver oil vs. control	↓ Incidence of disease	Holmes et al. (1932)
Children	160	New York	Halibut-liver oil vs. carotene vs. control	No effect on incidence of disease	Hess et al. (1933)
Children	575	Peterhead	Vitamin A + D vs. placebo	No effect on incidence of disease	Sutherland (1934)
Children	75	Loma Linda	Halibut-liver oil vs. vitamin A diet vs. control	↓ Severity of disease, ↑ weight gain	Gardner and Gardner (1934)
Adults	36	New Orleans	Cod-liver oil vs. historical controls	↓ Incidence and ↓ severity of disease	Beard (1934)
Adults	241	Cleveland	Halibut-liver oil vs. vitamin D vs. control	No effect on incidence of disease	Shibley and Spies (1934)
Children	275	Brooklyn	Halibut-liver oil vs. vitamin D vs. control	No effect on incidence of disease	Gittleman and Wiener (1935)
Adults	200	West Virginia	Various sources vitamin A vs. control	No effect on incidence, ↓ severity	Cameron (1935)
Children	262	Long Beach	Halibut-liver oil vs. historical controls	↓ Incidence of disease	Tress (1935)
Adults	1780	United States	Cod-liver oil vs. control	↓ Incidence of disease	Holmes et al. (1935)
Adults	3031	United States	Cod-liver oil vs. control	↓ Incidence of disease	Holmes et al. (1936)
Infants	104	New York	High vs. low vitamin A	No effect on incidence of disease	Lewis and Barenberg (1938)
Adults	54	Chicago	Vitamin A vs. vitamin D vs. vitamin A + D	↓ Incidence, severity in vitamin A + D group	Spiesman (1941)
Prevention of dental caries					
Children	102	Sheffield (?)	Three levels of vitamin A intake	↓ Incidence of disease	Mellanby et al. (1924)
Children	430	Rochester	Vitamin A + D vs. control	No effect on incidence of disease	Day and Sedwick (1934)
Prevention of puerperal sepsis					
Gravid women	550	Sheffield	Cod-liver oil vs. control	↓ Morbidity	Green et al. (1931)
Gravid women	235	Bellshill	Serum vs. adexolin vs. both	↓ Morbidity	Cameron (1931)
Prevention of skin infections					
Infants	118	London	Vitamin A vs. control	↓ Incidence of skin infections	Mackay (1934)

working days were lost per year to illness. Arthur Holmes, medical advisor to the E. L. Patch Company in Boston, calculated that colds and respiratory diseases cost American industries a waste of wages of exactly $494,836,363.68 per year (Holmes et al. 1936). About half of the industrial absenteeism was due to respiratory illness. Holmes and colleagues conducted a trial of cod-liver oil among industrial workers in a factory in the American midwest. Over 300 workers received daily cod-liver oil or no treatment, and the trial included both clerical workers and light- and heavy-machine operators. The outcome of the study was hours of industrial absenteeism due to respiratory illness. Members in the treatment group had 40% lower absenteeism than the control group (Holmes et al. 1932). A larger trial involving 1800 workers (Holmes et al. 1935) and another with over 3000 workers were reported (Holmes et al. 1936), and these studies suggested that cod-liver oil therapy reduced industrial absenteeism by two-thirds. Thus, cod-liver oil, which was very inexpensive, was considered to have tremendous value in saving millions of dollars in lost working days and lost productivity to American industry.

Measles. Throughout the nineteenth century, there were large measles epidemics in London which occurred about every 2 yr. During these measles epidemics some of the wards in hospitals in London would be overflowing, and up to 20% of children could die. Measles was generally considered to be unavoidable, and treatment of measles was largely supportive, with general hygiene and nursing. Respiratory disease and diarrhea often complicated a measles attack. Joseph Bramhall Ellison, an assistant medical officer with the London Fever Hospital, cared for children on the measles wards and was aware of the work of Edward Mellanby. Because vitamin A deficiency was shown in experimental animals to affect epithelial surfaces and the respiratory tract, Ellison reasoned that administration of vitamin A might be used to treat acute measles in children. Prior to his study, Ellison reported that the mortality rate from measles in the Acute Fever Hospitals in London was about 8% in 1929 and 1930. The following 2 yr, Ellison conducted a trial of cod-liver oil for 600 children with acute measles, and he randomized the children by ward in order to make the treatment groups comparable. Treatment with vitamin A reduced measles mortality by about one-half, from 8.7% in the untreated group to 3.7% in the treated group (Ellison 1932). Ellison's findings attracted a great deal of

TABLE 2

Studies of vitamin A as "anti-infective" therapy for specific diseases, 1920–1940

Subjects	*n*	Location	Intervention	Therapeutic effect of vitamin A	Reference
Therapy for acute measles					
Children	600	London	Cod-liver oil vs. control	↓ Morbidity and mortality	Ellison (1932)
Children	697	London	Cod-liver oil + vitamin D vs. vitamin D vs. control	No effect on morbidity or mortality	Mackay et al. (1936)
Therapy for pneumonia					
Mine laborers	299	Johannesburg	Cod-liver oil vs. ox liver vs. control	↓ Mortality	Donaldson and Tasker (1930)
Mine laborers	764	Johannesburg	Vitamin A vs. control	No effect on morbidity or mortality	Orenstein (1932)
Therapy for scarlet fever					
Children	509	Boston	Cod-liver oil vs. historical controls	No effect on incidence of complications	Sutliff et al. (1933)
Children	90	Madrid	Vitamin A vs. sesame oil vs. control	No effect on incidence of complications	Arjona (1934)
Therapy for typhoid fever					
Children	71	Marseille	Cod-liver oil vs. historical controls	↓ Morbidity and mortality	Giraud and Vallette (1939)
Therapy for tuberculosis					
Children	28	United States	Cod-liver oil vs. historical controls	↓ Morbidity, ↑ growth	Holmes and Ackerman (1930)
Children	78	Sheffield	Cod-liver oil vs. high vitamin A + D	Similar improvement in both groups	Pattison (1930)

attention, but some did not find consistent benefit in using vitamin A for measles (Gunn 1935).

Ellison's study was conducted at a time when case fatality rates for measles appeared to be falling in both Great Britain and the United States. For example, in Brighton (United Kingdom), only about 1% of children who developed measles died (Forbes 1933), and in large cities in the United States, the case fatality rate for measles had dropped to about 2% by 1930 (Emerson 1934). Helen Mackay, who studied nutritional problems in children, was on the staff of the Medical Research Council at the time when Edward Mellanby was serving as secretary of the council. Mackay conducted a second investigation of vitamin A therapy for acute measles. Her study was conducted among nearly 700 children admitted to the North Eastern Hospital in London in 1934. The overall mortality in the study was about 5%, and cod-liver oil had no apparent effect on reducing measles mortality (Mackay et al. 1936). The second negative trial seems to have dampened enthusiasm for using vitamin A as therapy for acute measles. In subsequent years there was infrequent mention of vitamin A in review articles and textbooks concerning the treatment of measles.

Puerperal fever. Another major challenge in the 1920s was puerperal fever, a common, fulminating bacterial infection that occurred among women who had just given birth. In the mid-nineteenth century, Oliver Wendell Holmes and Ignaz Semmelweis showed that puerperal fever was contagious and that doctors and midwives could spread the disease from person to person. The main bacterial pathogen involved in puerperal fever was later identified as a streptococcus. Careful hand washing was shown to lower the incidence of the disease and reduce maternal mortality. Even with these precautions, the case fatality rate from puerperal fever could be high. For example, in a large case series of women with puerperal fever reported from Glasgow, the mortality rate was about 5% (Thomas 1930). Antistreptococcal serum was evaluated in clinical trials for the treatment of puerperal fever, but there was little agreement whether it had any therapeutic value (Colebrook 1935).

While other investigators were directing efforts toward testing vitamin A therapy for the common cold, Mellanby and his colleagues conducted a trial of cod-liver oil therapy for puerperal fever in Sheffield. Their preliminary studies suggested that vitamin A therapy would reduce the morbidity and mortality of puerperal infection (Mellanby and Green 1929). From a small group of women with puerperal fever, they reported that 92% of control women died, whereas 29% of the vitamin A-treated women died, about a two-thirds reduction in mortality. Mellanby and his colleagues also thought that vitamin A could be used as prophylactic therapy against puerperal fever. In two hospitals in Sheffield, 550 women were enrolled during antenatal care to receive cod-liver oil or no treatment on a daily basis for 1 mo prior to delivery. The results of the trial suggested that cod-liver oil reduced the incidence of the most serious cases of puerperal fever from 4.7 to 1.1% (Green et al. 1931).

Physicians at the County of Lanark Maternity Hospital near Edinburgh conducted a large trial that confirmed the findings of Green and Mellanby (Cameron 1931). Treatment with cod-liver oil reduced the incidence of puerperal fever by an impressive two-thirds. The study was presented at the Edinburgh Obstetrical Society. In the ensuing discussion, one physician suggested that the findings were so good that application should be considered for maternity hospitals across the country, but others warned that further investigation was needed. In the puerperal fever wards of Belvidere Hospital in Glasgow, Scotland, 800 patients were treated with different therapies, including quinine, glycerin, sera, arsenicals, mercury, saline lavage, and vitamin A, and vitamin A did not appear to confer any advantage. It was argued, in any case, that

puerperal sepsis was not a nutritional deficiency disease (Thomas 1930).

ADVENT OF THE SULFA ANTIBIOTICS

The paradigm that vitamin A had an effect in reducing the severity of infections was still being worked out in the late 1930s. The development of the powerful sulfa antibiotics probably slowed further interest in the use of vitamin A as "anti-infective" therapy. Sulphonilamide treatment reduced the mortality from puerperal fever from 22 to 8% (Colebrook and Kenny 1936), and similar impressive results were obtained using sulfapyridine for lobar pneumonia. Much activity in clinical trials focused upon sulfa antibiotics and then later shifted to penicillin (Dowling 1977). The impact of antibiotic treatment upon infections was widely recognized, and vitamin A faded from the arena of clinical investigation. From 1940 onward, there were only occasional trials of vitamin A until the flurry of activity in the 1980s that was largely sparked by the observation of increased mortality among children with mild vitamin A deficiency in Indonesia (Sommer et al. 1983).

STATISTICAL INFERENCE AND CLINICAL TRIALS

The early investigations of vitamin A were, in essence, clinical trials, but they often lacked many features that are considered critical to the modern controlled clinical trial such as randomization, masking, placebo controls, and sample size and power calculations. The studies were also conducted in a period before the controlled clinical trial—as it is known today—became the widely accepted scientific basis for therapeutic experimentation (Marks 1997). Many ideas of statistical inference were just emerging in Great Britain and had little impact on the early clinical investigations of vitamin A. Jerzy Neyman and Egon Pearson (1928) introduced the idea of alternative hypotheses and two types of error. In their theory, Neyman and Pearson presented the idea of the probability α of rejecting a true hypothesis and the probability β of accepting a false hypothesis. To test a certain hypothesis, it is desirable to have a sufficiently large power function so that the probability α is small and the true hypothesis is accepted. The optimal experiment will thus utilize a sufficiently large sample so that the chance of the two types of error is minimized. If the rate of an outcome event is low, a large sample size is needed to detect with sufficient power if an experimental therapy is having an effect. For example, to show a reduction of mortality in measles from 4 to 2%, a clinical trial of vitamin A therapy in the 1930s would need to enroll at least 3000 children with measles to have sufficient statistical power to detect such a therapeutic effect on these low rates of mortality.

Although most of the early clinical investigations of vitamin A employed groups of untreated patients who served as controls, almost all of the trials lacked randomization, the assignment of patients on a random basis to treatment and control groups. The idea of randomization in experimental design was promoted by Ronald A. Fisher, a geneticist and statistician who began work at the Rothamsted Experimental Station in Great Britain in 1919. Fisher worked with plants, and he had some practical experience working as a subsistence farmer prior to entering academia. Fisher was put in charge of experiments to evaluate new grain varieties, and he was concerned about the design of previous experiments in which plots of grain were planted and compared. Fisher knew that the yield of two fields could vary because of differences in soil, temperature, light, moisture and other factors. As a solution,

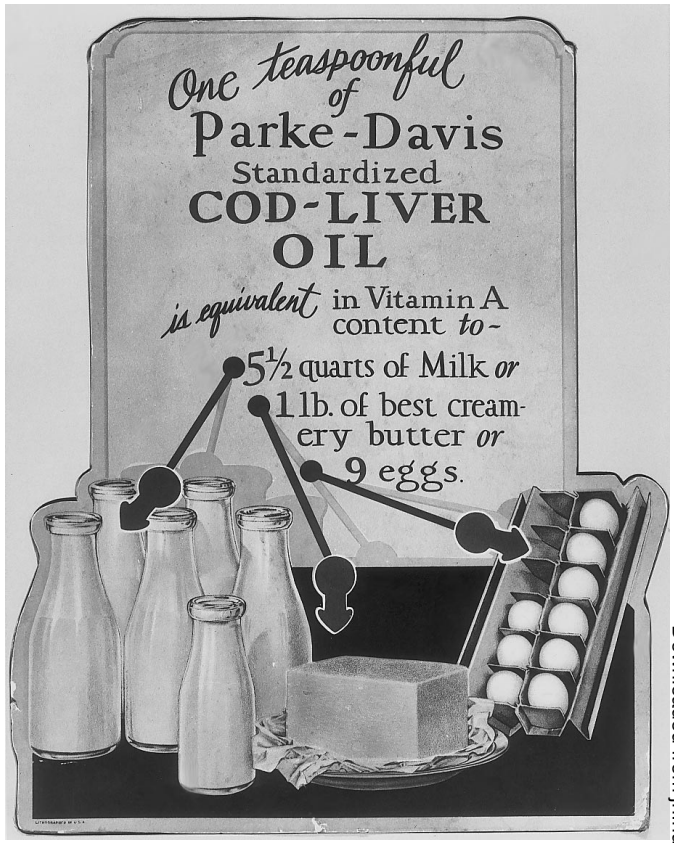

FIGURE 1 Folding counter display advertisement for Parke-Davis cod-liver oil, circa 1935 (Collection of the author).

Fisher proposed randomization of grain varieties by row, rather than by field, in order to reduce background variation in the experimental design. The idea of randomization was further promulgated by Fisher (1935) in his textbook *The Design of Experiments*, but there seemed to be little immediate effect upon clinical investigation. Randomization is often considered to have been introduced by A. Bradford Hill in British studies of streptomycin in the 1940s (Hill 1990), but it is apparent that the concept of randomization, either by individual or ward, was known at least to some clinical investigators in the vitamin A trials of the 1930s.

VITAMINS AND THE PUBLIC

The pharmaceutical industry was quick to promote the paradigm of vitamin A as "anti-infective" therapy. They aimed their advertising at young mothers in women's magazines using a combination of fear, hope, guilt, and the contemporary image of motherhood (Apple 1996). Advertisements warned mothers that the hidden danger of vitamin deficiencies could be lurking in their own homes. One ad read: "A certain famous American doctor, whose life is being devoted to the study of malnutrition in children . . . tells mothers that one out of every three children in the United States is malnourished." Another ad raised the question: "Your family vitamin-starved? Impossible! Yet science now finds the average American family diet lacking in at least 3 important vitamins!"

The work of Mellanby, Ellison and others did not go unnoticed by the pharmaceutical industry. A Squibb advertisement for cod-liver oil read: "Whooping cough, measles, mumps, chicken pox, scarlet fever may do greater harm than

most mothers think . . . the children will have lighter cases, they recover quicker and are less likely to be left with some permanent injury, if they build up good general resistance in advance to fight them . . . one precaution to build up the resistance of children . . . [is to give them] 'resistance-building' vitamin A. Vitamin A is the important factor which increases their fighting power in time of illness." The vitamin A content of some cod-liver oil preparations was impressively high **(Fig. 1).**

Vitamins occupy an unusual position in therapeutics, for unlike vaccines, antibiotics, or serum therapy, vitamins were more accessible by the public. Also the duality in vitamins exists: considered as a drug by some and as a constituent of food by others. Druggists attacked the grocers when bottles of vitamins started appearing on grocery store shelves, but the grocers argued that selling vitamins was consistent with selling fruits, vegetables and dairy products (Apple 1996). This "prophylactic and therapeutic weapon" of vitamins was placed squarely in the hands of the public, and whatever was thought by scientists could be accepted or rejected by the consumer. As a result of advertising and popular belief, the paradigm of vitamin A as an "anti-infective" vitamin became widely accepted by the public. By 1940, the United States and Great Britain alike had become extremely "vitamin-conscious." Legislation was proposed that miners and other workers could receive a larger ration of butter (British Medical Journal 1940), and milk was instituted as part of school lunch programs (Frazer 1950). With the outbreak of World War II, concern was raised over the crowded conditions of underground bomb shelters in London and the spread of respiratory and diarrheal disease. It was proposed that fortification of margarine with vitamin A would help to reduce the risk of infection (Lancet 1940). Cod-liver oil was provided by the British Ministry of Food for children under five and for pregnant and breastfeeding women (Kurlansky 1997). The administration of cod-liver oil became part of a morning routine for millions of children in America and Europe.

The theory that vitamin A influenced immunity and could be used as "anti-infective" therapy was clearly stated by Edward Mellanby, and his studies provided a model for a tradition of scientific research that continues today. The controlled clinical trial had evolved considerably since the 1940s (Marks 1997), providing what was considered the necessary scientific "proof" for the validity of particular therapies. In calling vitamin A the "anti-infective" vitamin, Mellanby (1934) noted, "we were, of course, aware of the drawbacks of giving a label of this kind, because the word 'infection' covers several different types of pathological phenomena, but we also recognized that it had the advantage of attracting the attention of workers to this important subject." After a pause of almost 50 yr, the value of vitamin A as "anti-infective" therapy was addressed again in controlled clinical trials, and these studies provided compelling new scientific evidence for the use of vitamin A as an important public health intervention.

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