History of Nutritional Immunology: Introduction and Overview[1]

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ABSTRACT Nutritional immunology is a newly recognized subdiscipline of vast clinical and public health importance. Its history began in 1810 with recognition of lymphoid tissue atrophy due to malnutrition. Discovery of vitamins in the early 1900s was followed by reports on their contribution to immunity and other host defenses. A hiatus in immunonutritional progress occurred during World War II and the "antibiotic era," but a worldwide rebirth of interest began in the 1960s and early 1970s. The current logarithmic growth of nutritional immunology was triggered by increased medical interest, plus the introduction of new concepts and investigative research methodologies from both parent sciences. J. Nutr. 122: 591–596, 1992.

INDEXING KEY WORDS:

- *nutrition* • *immunology* • *vitamin*
- *micronutrient* • *protein energy malnutrition*

Nutritional immunology, or immunonutrition, is a newly recognized scientific subdiscipline interrelating the seemingly disparate fields of immunology and nutrition. But despite their apparent independence, myriad observations, some quite old and some quite new, clearly show that the immune system cannot function optimally if malnutrition is present. Malnutrition also produces adverse effects on antigenically nonspecific mechanisms of host defense.

The clinical and public health importance of nutritional immunology is also receiving attention. Immune system dysfunctions that result from malnutrition are, in fact, Nutritionally Acquired Immune Deficiency Syndromes (NAIDS). NAIDS afflicts millions of people in the Third World, as well as thousands in modern centers, i.e., patients with cachexia secondary to serious disease, neoplasia or trauma.

As estimated during the 1990 World Summit for Children at the United Nations, attended by President George Bush and more than 50 other heads of state, 40,000 deaths occur each day worldwide in children under the age of five. Because malnutrition is the common denominator in most of these deaths, it must be assumed that NAIDS is playing its deadly role.

On the brighter side, however, and unlike the much more highly publicized acquired immune deficiency syndrome (AIDS), i.e., virus-induced AIDS, the immunological dysfunctions of NAIDS can generally be reversed quickly by correcting the nutritional problems that allowed NAIDS to develop in the first place.

Emergence of nutritional immunology as a new scientific subdiscipline of vast public health and clinical importance naturally raises questions about its historic origins (1, 2), which are linked closely to scientific findings in both parent sciences. Key early discoveries in these sciences are listed in **Table 1**.

HISTORICAL EMERGENCE OF NUTRITIONAL IMMUNOLOGY

As in the history of most sciences, scattered, sporadic observations came first. Only in retrospect did these gain historic importance. These were followed by planned studies, which at first were neither broad nor systematic in their design or impact. Momentum gained in immunonutrition during the "vitamin era" was lost during World War II and the "antibiotic era".

In a rebirth of interest, numbers of involved scientists and their reports began to increase during the 1960s (2). Research in nutritional immunology then

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TABLE 1

Pre-1935 discoveries (and scientists) in nutrition and immunology

Date	Nutritional discoveries	Immunological discoveries
1721		Smallpox immunization (Montague and Broylston)
1757	Antiscoubutic value of lemons (Lind)	
1798		Cowpox virus for immunization (Jenner)
1810	Thymic atrophy due to malnutrition (Menkel)—The Birth of Nutritional Immunology	
1833	Digestive process details (Beaumont)	
1865	Xerophthalmia (Lobo & Teuscher)	
1880		Attenuated organism vaccines (Pasteur)
1882	Beriberi and its therapy (Takaki)	
1884		Phagocytosis (Metchnikoff)
1890		Bacterial toxin antiserum (von Behring)
1894		Complement (Buchner)
1897		Basic concepts of immunology (Ehrlich)
1900		Complement fixation reactions (Bordet)
1902	Laws of energy consumption (Rubner)	
1906	Need for trace nutrients (Hopkins)	
1909	Indispensibility of lipids (Stepp)	
1910		Anaphylactic reactions (Riched)
1911	Isolation of a vitamine, thiamine (Funk)	
	Broad nutritional studies (Osborn & Mendel)	
1914	Isolation of riboflavin (Goldberger)	
1916	Vitamin A (McCollum)	
1922	Vitamin E (Evans & Bishop)	
1928	Vitamin C in adrenals (Szent-Gyorgi)	
1930		Human blood types (Landsteiner)
1931	Kawshiorkor in children (Williams)	
1934	Vitamin C synthesis (Reichstein et al.)	

entered logarithmic growth in the 1970s (1, 2). However, close working relationships between researchers from both parent sciences have rarely been achieved (1, 3).

EARLY OBSERVATIONS

Writings from antiquity include Egyptian, Indian, and biblical admonitions about foods and health and clear instructions by Hippocrates that physicians must evaluate the diet to understand disease (2, 4). Although of historical interest, such ancient observations fail to provide any clear evidence for an adverse impact of malnutrition on the immune system itself. Nevertheless, the ancient Greeks clearly understood the concept of immunity. In the well-known mythological tale, the infant Achilles was dipped in waters of the River Styx to immunize him from future battlefield injury. If this myth portrays a valid early concept of immunization, then the Achilles Heel might be considered the first recorded instance of an immunological dysfunction.

The earliest scientific evidence for a direct link between cachexia and immunological dysfunction resides in observations of lymphoid tissue atrophy in the face of severe malnutrition (2). As cited by Jackson (5), J. F. Menkel was the first, in 1810, to describe thymic atrophy in malnourished patients. Menkel's linking of malnutrition and thymic atrophy constitutes the scientific birth of nutritional immunology. In 1845, J. Simon (6) called the thymus, "a barometer of malnutrition, and a very sensitive one." "Nutritional thymectomy" then became a common medical term. This anatomical link between nutrition and immunology was recognized long before the thymus was found to be of key immunological importance, and a full half century before Paul Ehrlich developed the basic concepts of immunology or Max Rubner defined the basic laws of energy consumption in nutrition and metabolism (Table 1).

THE VITAMIN ERA

Early observations (Table 1) concerning the vital importance of nutrients in citrus fruit, rice polishings, milk and lipids introduced the vitamin era, which began early in this century. Isolation of thiamine by Funk in 1911 led him to coin the term vitamine (i.e., vital amine) (1, 2), but the final e was discarded when it was found that other vitamins were not amines. It was recognized quite early that both vitamin A and vitamin C had unique antiinfective properties (1), but their linkages to immunological mechanisms remained unknown until later decades.

Discovery of vitamins and increasing knowledge about nutrition aroused much medical and public in-

terest in the 1920s and 1930s. Before the discovery of antibiotics, the outcome of severe infections often depended on the excellence of supportive care, which included, importantly, a fully nutritious diet.

The vitamin era peaked with the classical text by Perla and Marmorston (4), *Natural Resistance and Clinical Medicine*. This impressive work encompassed the immune system and other host defenses, along with a review of the roles of protein, energy, lipoids (as then spelled), vitamins and minerals in body resistance mechanisms. If immunonutritionists had existed during the vitamin era, Perla and Marmorston's book would have been their principle reference source.

THE WORLD WAR II YEARS

In the chaos of war, little fundamental research of immunonutritional importance emerged, but a book, *Hunger Disease* (7), made many important clinical contributions. During the prolonged siege of the Jewish ghetto in Warsaw by the Nazi army, Israel Milejkowski (the ghetto's public health officer) encouraged a group of 28 physicians to describe clinical findings in their own specialty areas, concerning the medical effects of slow starvation faced by the siege victims.

After the war, surviving manuscripts were published, but because of limited availability, they remained virtually unknown in the West. Eventually, copies were obtained by Myron Winick (7), who had them translated and republished as a book.

Although thousands of ghetto deaths came from tuberculosis or typhus, $\geq 15\%$ of autopsies showed deaths due to starvation alone. Medical findings in cachexia were recorded in patients with no other overt disease or infection. Ghetto physicians apparently did not know of Cicely Williams' description of kwashiorkor in 1931 (Table 1), but they wrote of hunger edema and marasmus in children under five, none of whom survived prolonged starvation. Atrophy of lymphoid tissues, loss of dermal reactivity to tuberculin, low white blood cell counts with neutropenia and an absence of eosinophils and a loss of gastric acid were found in adults. Cachexia was also shown to cause a loss of clinical allergies, including asthma, hay fever and dermal or food hypersensitivities.

THE ANTIBIOTIC ERA

Discovery of gramicidin by Rene Dubos in 1939 and the clinical use of penicillin (discovered by Alexander Fleming in 1929) led to the antibiotic era, which reached full swing during the 1950s. Growing availability of antibiotics and concomitant breakthroughs in other medical sciences became of overwhelming importance. In contrast, interest in the supportive and nutritional aspects of medical care reached a nadir in the late 1940s and 1950s.

In this immunonutritionally bleak period, the work of Abraham E. Axelrod, of the University of Pittsburgh, has the solitary brilliance of a shining beacon in an otherwise dark sky. Axelrod's work on the effects of vitamins on immunity first appeared in 1947 and continued for many decades into the 1980s. Assisted by a long succession of graduate students,[3] Axelrod set the stage for future immunonutritional researchers by his carefully designed experiments and his consistent use of the best available techniques of both immunology and nutrition.

THE NEW BEGINNINGS

In the 1960s and early 1970s, a reemergence of interest in nutritional immunology became evident, as clinical and basic research studies were begun in more than 25 different countries (see **Table 2**). Perhaps stimulated by two World Health Organization publications (8, 9) [especially the widely quoted monograph by Scrimshaw et al. (8)], many scientists became involved (Table 2). Although some individuals made only a limited commitment, many groups, especially those with a sufficient critical mass, began to make long-term contributions to immunonutritional progress. Among the most prominent were research groups working in India, at Chiang Mai in Thailand, in South Africa, Nigeria, and other countries of Africa and at the INCAP laboratories in Guatemala. Studies in the Western world were focused in the British Isles and in a number of institutions in the United States.

During this period of immunonutritional reemergence, work on vitamins was continued by Axelrod (2) and in a series of unique and important studies in volunteers conducted by Robert E. Hodges and his associates (2) at the University of Iowa (Table 2). However, most attention during this period of new beginnings focused on effects of protein-energy malnutrition and of iron deficiency (or excess) on the immune system and other host defensive mechanisms. Other important stimuli to immunonutritional progress included the surgical introduction of techniques to provide total parenteral hyperalimentation to malnourished patients (2) and the demonstration in many studies that NAIDS could be reversed by appropriate nutritional therapies (2).

[3] Abraham E. Axelrod's coauthors (arranged alphabetically) include the following: H. Bloch, N. Calvanese, B. B. Carter, B. Fisher, E. R. Fisher, R. Geisinger, E. C. Hamill, S. Hopper, A. M. C. Koros, M. Kumar, S. H. Lee, Y. Chiung Puh Lee, D. A. Long, P. P. Ludovici, J. Pruzansky, D. J. South, W. R. Stinebring, A. C. Trakatellis, and P. Walsh.

TABLE 2

The geographic distribution of scientists (arranged alphabetically) who contributed in the 1960s and early 1970s to a rebirth of nutritional immunology

Location	Scientists
Boston	M. E. J. Beard, G. Edsall, S. N. Gershoff, T. J. Gill, E. J. Goetzl, G. T. Keusch, J. J. Vitale, L. R. Weintraub, M. Winick
Brazil	C. Marigo, R. Pinto Paes
Canada	R. K. Chandra, S. Chandra, D. Howse, O. P. Ghai, K. M. Kutty, A. K. Saraya, D. Vyas
Chile	L. Grez, G. Heresi, A. Ohlbaum, L. Schlesinger, A. Stekel
Colorado State Univ.	P. A. Campbell, R. H. Heinzerling, C. F. Nockels, R. P. Tengerdy
Columbia	L. Echeverri, D. Franko, M. A. Reyes Reyes, N. G. Saravia
Denmark	J. Clausen, J. Moller
Egypt	I. I. Araby, G. H. Aref, M. K. Badr de Din, A. I. Hassan, K. Kamel, S. Shousa
England	J. J. Bullen, H. M. Coovadia, A. J. S. Davies, A. E. Dolby, E. P. Faulk, E. J. Field, J. Fletcher, E. Griffiths, P. S. E. G. Harland, A. F. Hoffbrand, B. E. C. Hopewood, D. Hughes, R. Hunt, A. Jacobs, D. H. M. Joynson, H. McFarlane, C. J. Meade, J. Mertin, J. Ring, H. J. Rogers, J. Seifert, B. K. Shelton, J. F. Soothill, E. Tripp, P. R. Uldall, D. M. Walker, J. L. Waterlow, R. Wilkinson
France	A. Aschkenasy, M. Dardenne
The Gambia	I. A. McGregor, R. G. Whitehead
Germany	E. A. Guthy, J. R. Kalden
Ghana	K. C. Rich, C. G. Neumann, E. R. Steihm, M. Swenseid
Guatemala	J. Alvarado, G. Arroyave, V. Argueta, M. Beher, G. Casteneda, S. D. Douglas, R. Fernandez, B. Garcia, O. Guerrero, G. T. Keusch, R. A. Kromal, A. Lechtig, L. J. Mata, J. B. Salomon, M. Sanchez, R. E. Schneider, N. W. Solomons, C. Tejada, J. J. Urrutia, E. Villatoto, F. Viteri
India	C. Bhaskaram, R. A. Bhujwala, R. K. Chandra, O. P. Ghai, S. Krishnan, K. A. V. R. Krishnamachari, S. Mishra, M. Monanram, J. S. Prasad, V. Ramalingaswami, V. Reddy, A. K. Saraya, S. V. Seth, S. Sharm, S. G. Srikantia, G. P. Talwar
Indiana Univ.	E. D. Weinberg
Indonesia	L. J. Casazza, M. Sugiono, S. Sunoto
Iowa State Univ.	M. A. Kenny, J. L. McGee, F. Piedad-Pascual
Ivory Coast	S. D. Douglas, L. Matter, K. Schopfer
Jamaica	B. Golden, M. H. N. Golden, A. A. Jackson, J. Patrick, D. Picou, J. C. Waterlow
Johns Hopkins Univ.	B. G. Bang, F. B. Bang, R. E. Black, K. H. Brown, A. A. Kielmann, C. E. Taylor
Lebanon	R. Y. Asfour, Z. L. Awdeh, S. S. Najjar, M. Stephan
Massachussets Inst. Tech.	R. B. Baggs, R. K. Chandra, J. E. Gordon, R. L. Gross, C. E. Hunt, S. A. Miller, D. P. Nelson, P. M. Newberne, J. V. O. Reid, N. S. Scrimshaw, E. A. J. Williams, G. Williams, R. B. Wilson, V. R. Young
Mexico	B. L. Nichols, S. Frenk, J. Kumate Rodriguez, C. de la Pena, R. R. Watson
New York Univ.	B. Benacerraf, A. Berken
Nigeria	J. F. Adcock, A. U. Antia, O. Longe, H. McFarlane, S. Reddy, L. S. Salimonu, J. F. Soothill
South Africa	C. G. Brereton-Stiles, E. Bhettay, S. Cohen, H. M. Coovadia, J. D. L. Hansen, M. P. Keet, W. E. K. Loening, L. J. Madcougall, A. Mafoyane, O. L. Meyers, M. A. Parent, P. J. Pretorius, M. Schonland, E. Sellmeyer, B. C. Shanley, P. M. Smythe, H. Thom, A. S. Truswell, L. S. de Villiers
Thailand	C. Asvapaka, C. Charupatana, D. Damrongsak, R. Edelman, P. Kulapongs, C. Leitzmann, R. E. Olson, S. Sirisinha, R. M. Suskind, O. Thanangkul, V. Vithayasai
Tulane Univ.	N. R. DiLuzio
Tunesia	B. Hamza, S. Khadroui, V. Lopez, N. J. Smith
Uganda	R. E. Brown, M. Katz, T. Watts
Univ. Arizona	M. Chvapil
Univ. Chicago	J. Metcoff, T. Yoshida
Univ. Cincinnati	J. W. Alexander, J. D. Stinnett
Univ. Florida	R. Ganguli, B. M. Gebhardt
Univ. Iowa	W. B. Bean, R. E. Bleiler, R. E. Hodges, M. A. Ohlson
Univ. Minnesota	W. C. Cooper, S. D. Douglas, G. Fernandes, R. A. Good, D. G. Jose, E. Yunis
Univ. Pennsylvania	N. I. Abdou, J. Daly, S. J. Dudrick, D. K. Law
Univ. Pittsburgh	A. E. Axelrod and associates listed in footnote 3
Univ. Texas	M. Jurin, I. F. Tannock
Univ. Washington	L. C. Robson, M. R. Schwarz
USA Med. Res. Inst. Infect. Diseases	W. R. Beisel, C. C. Berdgis, J. A. Bellanti, P. C. Canonico, R. D. Feigin, I. Gray, R. H. Herman, R. J. T. Joy, A. S. Kleiner, R. S. Lees, G. Lust, H. A. Neufeld, R. S. Pekarek, M. C. Powanda, M. I. Rapoport, W. D. Sawyer, G. E. Shambaugh, R. L. Squibb, R. W. Wannemacher, K. A. Woeber
Wales	A. E. Dolby, A. Jacobs, J. H. Jarvis, D. H. M. Joynson, D. M. Walker
Wayne State Univ.	P. Frost, A. S. Prasad

TABLE 3

Major meetings on nutritional immunology

Date	Place	Meeting	Organizer(s)	Sponsor
1975	Santa Ynez, CA	Workshop on Malnutrition and Immunity	Subcommittee on Nutrition and Infection, Food, and Nutrition Board	National Academy of Science/National Research Council and The Kroc Foundation
1978	Bethesda, MD	Conference on Nutrition and Immunity	Robert Edelman Robert A. Good	National Institutes of Health
1979	Atlanta, GA	Workshop on Single Micronutrients and the Immune System	William R. Beisel	Nutritional Advisory Board, American Medical Association
1981	Bethesda, MD	Workshop on Trace Element Regulation of Immunity and Infection	Ranjit K. Chandra Deborah H. Dayton	National Institutes of Health
1984	St. Johns, NF	Conference on Nutrition, Immunity, and Illness in the Elderly	Ranjit K. Chandra	International Union of Nutritional Sciences, University of Newfoundland, Medical Research Council
1987	Toronto, ON*	Satellite Symposium on Nutrition and Immunity	Ranjit K. Chandra	International Union of Immunological Societies
1989	New York, NY*	Conference on Micronutrients and Immune Functions	Adrianne Bendich Ranjit K. Chandra	New York Academy of Sciences
1989	Minneapolis, MN	Symposium: Update on Immunonutrition	Jerome LiCari	Sandoz Nutrition Corporation

* Open meeting.

LOGARITHMIC GROWTH OF NUTRITIONAL IMMUNOLOGY

The enthusiasm and research generated by increased numbers of investigators led to an upsurge in the number of immunonutritional publications. A logarithmic phase of growth was reached by the early 1970s (1, 2). Interest in nutritional immunology was also stimulated by a number of conferences or workshops held in the late 1970s and 1980s. These are listed in **Table 3**.

Another stimulus to the increased current interest in, and growth of, nutritional immunology was the publication of a number of important books and monographs (1, 3, 10–18). Several of these covered the presentations and discussions of papers delivered during conferences listed in Table 3 (1, 3, 10, 13). Some focused on specific aspects of immunonutrition, i.e., relationships to infection (8, 11, 14) the roles of specific micronutrients (1, 3, 13), including the antioxidant nutrients (18), or on immunonutritional problems in elderly people, whereas others attempted to define and analyze the unique relationships of malnutrition to immunological dysfunctions (1, 10–12, 14, 16–18).

Still another ongoing stimulus to progress has been the formation of an International Nutritional Immunology Group (INIG), which came into being at the Federation of American Societies for Experimental Biology meeting in 1980. This initially informal group was organized and continuously sustained by Ranjit K. Chandra, who has emerged progressively as the current leader of the immunonutritional field, with his broad research studies [Table 2], books (1, 11, 12, 15, 17) and organizational abilities [Table 3].

To complete this introductory overview, it must be noted that in mid-1991 a new publication will make its debut, *The Journal of Nutritional Immunology*, with Julian E. Spallholz as its editor-in-chief. When a new subdiscipline has its own journal, it may be said to have come of age. Hopefully, that is now true of nutritional immunology.

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