



The Thymus Letter

The story of the discovery of the crucial role of the thymus in mammalian immunity:1952-1962

in memoriam **Robert A. Good** *Primus inter pares*

'Quidedit beificium taceat; marret qui accepit'

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Introduction

Mihi cura future

In the process of preparing the Robert A. Good archives and society, it has come to our attention that there have been debatable published comments regarding the first demonstration of the crucial role of the mammalian thymus in immunity .
[1,2,3,4,5,6,41,32,42,43](#), To hear Dr. Good tell the thymus story, in his own words, please refer to the section on Scientific Contributions on his webpage to listen to a 1964 lecture on the thymus, preserved in MP3 format. www.RobertAGoodArchives.com .

'it is our responsibility to keep the literature straight'

Robert A. Good

The Story of the Thymus Discovery 1952

Alis volat propriis

Good's interest in the thymus, per se, as an organ crucial to immunity began in 1952². However, his interest in the plasma cell, antibodies and the immune response began in 1944, while still in medical school, at the University of Minnesota in Minneapolis, with publications beginning in 1945.^{2,14,33} It can be shown, that Good's work on the thymus, elucidating its crucial role in mammalian immunity, as a result of neonatal thymectomy experiments in the rabbit, was the first publication in the evidentiary chain of proof of discovery. The results were published in March of 1961 in the form of an AAI abstract, on experiments done during 1959 and 1960. The work was directed by Good and performed by his MSc student Olga K. Archer with the assistance of Varco's highly competent junior surgical fellow, James C. Pierce.^{2,8} The abstract, submitted, in December of 1960, by Good as a member of AAI precluded his authorship. This would be Good's second round of experiments on thymectomized rabbits, which began several years earlier, but the first published experimental evidence in successful demonstration of their earlier theory. The abstract was submitted contemporaneously with but prior to the work of Jacques Miller who brought attention to his work and equally compelling discovery with his publication of a preliminary communiqué in *The*

Lancet of September 30, 1961. Miller published on the demonstrated effect of neonatal thymectomy on the immune response in mice coming from a viral perspective while Good based his work on the appearance of thymoma with immunodeficiency.^{10,17} Indeed, the oft cited paper from Good's group did conclude that thymectomy in the *adult rabbit* had little or no statistically significant effect on antibody production. However, that was only part of what the authors had to say regarding their theory, despite the instant results. Selected excerpts from the respective author's papers misspeak the author's complete intent of their reporting. Taken out of context and without a full reading of the cited and more importantly a second contemporaneously published paper might lead the reader to a different conclusion and give superior credit to others.^{10,11,17,22,24} The following remark, has been cited as innuendo, that Good ,et al., had all but abandoned the thymus: 'the thymus gland does not participate in the control of the immune response'.¹⁰ However, in that same 1956 paper, first authored by Good's and Varco's students MacLean and Zak, the very first sentence boldly puts forth, as it directly relates to the human model, Good's theory that . '*The simultaneous occurrence of acquired agammaglobulinemia and benign thymoma, in a **human being**, suggested that the thymus might participate in the control of antibody formation.*¹⁷ In that paper, describing the clinical case of patient F.H. and results of the first rabbit thymectomy experiments, Good states that regardless of the results of the instant experiments, he still firmly believed, that the thymus was not just 'associated' with immunological deficiency but the phenomena of thymoma; an *epithelial* overgrowth of tissue, with agammaglobulinemia, in man, were related in some *essential* manner. In ,yet, another place: ' it still seems likely that some *essential* relationship exists between the thymic tumor and the acquisition of acquired agammaglobulinemia. A second case of acquired agammaglobulinemia with thymoma presents itself and 'strengthens the conviction that the two phenomena are related in some *essential* manner'¹⁷. Those early observations and diagnoses in patients later became known as 'Good's syndrome; immunodeficiency with thymoma. In the concluding paragraph, the authors state that *the' nature of the relationship awaits further investigation*'. Those statements indicate the authors conviction of the *essential* role of the thymus and were not white flags of surrender to the mysteries of the thymus! Good's group did, indeed, investigate further. The results of those later rabbit and mouse thymectomy experiments from his lab were submitted for publication in several journals beginning in December of 1960 with the AAI abstract.^{8,45,}

Both Good's group and Miller tested the scientific waters, albeit on different continents, with their preliminary published reports during 1961 and 1962. Good had been in pursuit of the mechanism of immunity since his plasma cell days of 1944 and studies on Hodgkin's and myeloma patients in 1949 and 1950.^{47,48} *. The role of the thymus in immunity began once he read Bruton's 1952 description of an 8 year old patient whose electrophoretic patterns was void of gammaglobulin and the 1953 clinical case of F.H., an adult patient with thymoma and acquired agammaglobulinemia.^{12,13,14,15,16,33,34,35} He followed the clinical presentations with the early rabbit experiments and his firm belief that the thymus was , *indeed*, an organ of importance in immunity. That opinion, to be repetitive, did *not* change regardless of the results of the first rabbit thymectomy experiments.

In statu quo

The AAI abstract was orally presented, by Archer, at the April 1961 FASEB meeting, in Atlantic City.^{2,8} This published work, representing the work of several people, was the consequence of many previous years of thought and experimentation. It is for these reasons, i.e. the first published rabbit thymectomy papers of 1954 and 1956 and even earlier theory positing the suspected crucial role of the thymus, that published work by others have been persuasive set against the well established facts as laid down by Good et al.. To split hairs re: Peer reviewed or not, uttered or not, communicated or not, does not carry, in our opinion, as much weight as the initial start date of scientific enquiry into the role played by the thymus.

Both Good and Miller did brilliant work in the field and what is more important is that, coming from different perspectives, i.e. viruses and thymoma, both men arrived at the same conclusion!

Good, never failed to give credit to and share with J.F.A.P. Miller, his esteemed younger fellow scientist and physician, their respective independent and yet contemporaneous discovery of the role of the thymus, as viewed in two different animal systems.² Good, always brought Miller to whatever podium behind which he stood or paper that he published on the subject and openly celebrated Miller's contemporaneous discoveries, while still maintaining that his lab was the first to publish.²

Genesis of the timeline as it relates to the thymus

1952

Good began his intellectual and experimental queries into related to the thymus in 1952 at the University of Minnesota, initially with pediatric patients. Good said that one morning in 1952 he 'opened his green pediatric journal' and found an article by Col. Ogden Bruton describing the electrophoretic pattern of an eight year old patient, seemingly, devoid of gamma globulin i.e., agammaglobulinemic.^{2,3,4} Good immediately thought of his experience at the Rockefeller during 1948 and 1949 with myeloma and Hodgkins patients and eagerly looked for an opportunity to test his theory, formed years previous, that these patients would be unable to form plasma cells (2). He was able to ascertain and then diagnose agammaglobulinemia in pediatric patients before he had the opportunity to consult on the famous, F.H., adult thymoma patient.^{12,13,15,16,35}

Shortly thereafter, in 1953, Good would be granted that opportunity in the form of an unique patient. His colleague Richard Varco, asked Good, even though a pediatrician, to consult on a 54 year old male patient who had initially presented to his chest clinic in June of 1951. The patient complained of, among other things, having suffered at least seventeen bouts of pneumonia during the previous eight years and a pronounced susceptibility to infection, which had increased, concomitant with the appearance and eventual extirpation, by Dr. Varco, of a benign, 565 gm. stromal epithelial anterior mediastinal thymoma.^{2,12,13,15,17} The interesting thing to Good, about this patient, was that he also carried a diagnosis of agammaglobulinemia. Pairing the dual diagnosis of thymoma with agammaglobulinemia Good described a new syndrome that would carry his name; Good's s.; thymoma with immunodeficiency.^{2,12,13,15,16,17} Extirpation of the

thymoma did not restore the patient's immunological competency^{2,12,13,15,16,17,23} Plasma cells, however, were not 'completely' absent. The patient was severely hypogammaglobulinemic rather than agammaglobulinemic. Lymphocyte numbers were low and defective homograft immunity was demonstrated by a slow and marked rejection of skin allografts.^{2,12,13,15,16,17,23} **Good says that it was at this point in time that they began to question the role of the thymus in immunity**²**This immunologic patient profile and that of others like him led to the first of many experiments on the thymus and thymectomies in young mammals.**^{1,2,7,9,25,26,27,28,29, 31,38,39}

This *new* syndrome was recognized as a result of the pairing of these two disease states: **Good's Syndrome** (thymoma with immunodeficiency) and is more completely described as a rare cause of combined B and T cell immunodeficiency in adults. The clinical characteristics of Good's syndrome are increased susceptibility to bacterial infections with encapsulated organisms and opportunistic viral and fungal infections. The most consistent immunological abnormalities are hypogammaglobulinemia and reduced or absent B cells.

*The association between the presence of a thymoma and immunodeficiency is credited by being first recognized in 1954 by Dr. Robert Good, who described a case of thymoma and hypogammaglobulinemia in an adult.*¹³

Good shares with his reader, in *The Minnesota Scene*, about the prevailing myopic views of the thymus, at that time, as an organ of little interest or consequence once the animal was birthed. He says he was reminded of Hebbel's warning that the thymus was a 'vestigial organ', that lacked an important role in immunity.² However, undaunted by such veiled scientific and myopic views, Good, MacLean, one of Varco's fellows and a medical student associate of Good's, Sol Zak set out to find out for themselves what role, if any, the thymus really did play in immunity. They relied on the work of Scannon and Boyd regarding the anatomy and physiology of the thymus^{2,18,19,20,21}

Under Good's direction, Zak and MacLean performed thymectomies on 4-5 week old rabbits, which was as young as they thought possible or necessary, at that time. The first experiments in the animal model, published in 1956 and 1957 did not demonstrate Good's postulate.^{11,17} Results showed no significant statistical effect on immunological function. . Good states 'in the discussion portion of the report containing the clinical association of thymoma and immunodeficiency they clearly stated that although the initial experimental results with rabbits, under those experimental conditions, had not been revealing, they still considered their '*Experiments of Nature*' as demonstrated, in fact, by their patient with both conditions, i.e. agammaglobulinemia as a form of immunodeficiency and thymoma to show that the thymus does, *indeed*, play a crucial role in immunity functions.^{2,17} The proof of their postulates would come a few years later.⁸

1958-1960

At a Spring, 1959 FASEB meeting. Good was impressed by a conversation he had with good friend and colleague Harold Wolfe, who sought him out after a presentation because he knew of Good's interest in the thymus and he wanted to share some exciting

news regarding his , colleague Meyer and student Mueller's recent work on neonatal bursectomy experiments in the chicken in their Wisconsin labs.^{2,23} In support of their work, he told Good about the earlier serendipitous findings of Bruce Glick et al. published in an 1956 *Poultry Science* article which had been first submitted and turned down by the journal *Science*, on the effect of neonatal bursectomy in the chicken and the lack of immune response.⁴¹ Upon hearing the exciting news, Good's, then, graduate student, Ben Papermaster went to Wolfe's labs in Wisconsin to find out more about their experiments. When Papermaster returned, Good, his colleagues and students immediately set about designing experiments with this new information in mind.. In 1959 and 1960, Good, Martinez et al. begin to take another look at the earlier published rabbit thymectomy experiments of 1956 and 1957.² Their theory or opinion on the important role of the thymus in immunity had not changed since that earlier time. In the new experiments, they would thymectomize the rabbit during the neonatal period.^{2,8,25} Led by Good's colleague, Carlos Martinez, trained in Argentina under Nobel Laureate Houssay , they also began neonatal thymectomy experiments in the mouse model.
^{27,28,38,39,43,44}

Good launched, then, Master's graduate student Olga K. Archer, with the assistance of Varco's young surgical fellow James C. Pierce, on thymectomizing rabbits from birth forward to several weeks of age.² The labs were a flurry of excitement and filled with various ongoing experiments The results of the new experiments, neonatal thymectomy in the rabbit, demonstrated Good's initial and long held postulate.^{2,11,17} Extirpation or prevention of the normal developmental sequence of the thymus resulted in an inability to make antibodies.^{8,25,26,27} or to develop the capacity to induce GVHD.²⁸ Good always reminded us that it is called research because things have to be repeated.

Facta, et verba

The first official publication, by Good's group, on these landmark experiments, on the thymus was, therefore, the previously mentioned abstract submitted to AAI, by Good as a member, in December of 1960, for later oral presentation by Archer at FASEB in Atlantic City. The following April of 1961. At that FASEB session, chaired by Good, he gave the audience, of over 100 immunologists, an in depth and complete update on the cited rabbit experiments. In addition, results were discussed that he, his colleague Martinez and their associates Kersey, Papermaster, Dalmasso et al. had gathered working in the, mouse, chicken, hamster and dog systems. The results of those neonatal thymectomy experiments demonstrated the prevention of normal development of both humoral and cell-mediated immunity. In the area of transplantation, rejection of homograft or allograft as well as allogeneic and syngeneic tumor formation was prevented. Good said that he, in his typically audacious manner said '*at long last we have now established once and for all that the thymus, indeed, plays an important role in immunity.*'² He further state that this finding was to make possible the normal development of **both** cellular and humoral immunities. (;*unpublished discussion, Robert A. Good, et al., annual meeting of the American Association of Immunologists, Atlantic City, New Jersey, April, 1961*) This statement was made after almost a decade of dedicated work on the thymus and its relationship to immunity.

Ipsa facto

The first completed, in depth, peer reviewed paper, with Good as a formalized author, to be sent forward was submitted to Proc. Soc. It was submitted during the late summer period; July/Aug of 1961. Due to a lengthy printer's strike, the paper languished either at or in press for several months. The net result was that the paper did not come out of press till January 5, 1962, months after submission! Were it not for the printer's strike, Good would have had both the abstract and Proc. Soc. Paper published during 1961. However, that was not to be. It was Jacques Miller's turn to publish first with his important paper on the analysis of the thymus and its influence in leukaemogenesis which came out of press on September 30th, 1961.⁴⁶

1962

Ab ovo usque ad mala

Good, once again, rose to the occasion of leadership as well as true to the spirit of sharing scientific information, and quickly convened the first international symposium on the thymus in November of 1962 in Minneapolis, Minnesota with the attendance of more than 100 investigators, 72 of whom presented their current work in immunobiology on the thymus and bursa. The book on the proceedings of that conference was dedicated to Harold Wolfe, Good's esteemed colleague who first told Good about Glick's work on the bursa at that 1959 FASEB meeting who passed away before its publication. The book, published in 1964 and entitled: The Thymus in Immunobiology: Structure, Function, and Role in Disease¹, is a 'must read' for those interested in the early years on work on the thymus and bursa and their roles in immunology.

Summary

Ipsa dixit

Good states: *'From our point of view, because of the initial abstract from our laboratory which preceded all the other publications, including Miller's Lancet paper, we felt the events clearly established our priority in the discovery of the thymus function.'*²

Ext modus in rebus ;

The important thing is, in some circles, the all important date of first publication in which case the award goes to Good for the abstract. Then, there is the question of first published full length paper. Miller's communiqué like Archer's abstract were not full length papers, nor were they intended to be; Archer's was an abstract and Miller's was a preliminary communiqué. Both reports made their debuts in scientific society in 1961 followed, by a plethora of substantial and more convincing papers. At the end of the day and asked who won? We would submit that everyone did.

Respectfully ,

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Robert A. Good Archives

The Thymus Letter

Bibliography

1

The Thymus in Immunobiology: Structure, Function, and Role in Disease

Edited by **Robert A. Good**, MD, PhD and Ann E. Gabrielsen, MA

Hoeber Medical Division, Harper & Row, Publishers

1964

ISBN: 64-19494

2

The Immunologic Revolution: Facts and Witnesses

Edited by Andor Szentivanyi and Herman Friedman

Ch. 9 *The Minnesota Scene: A Crucial Portal of Entry to Modern Cellular Immunology*,
by Robert A. Good

CRC Press 1994

ISBN: 0-8493-4722-X

3

Personal communication

Noorbibi-Day Good, PhD

St. Petersburg, Florida, May, 2005

4

Personal communication

Edmond Yunis, MD

Boston, MA, May 2005

5

Personal communication

Agustin Dalmaso, MD

Minneapolis, MN, Dec. 2004, May 2005

6

Personal communication

John Kersey (ck name)

Minneapolis, MN, May 2005

7

Good RA, Dalmaso AP, Martinez C, Archer OK, Pierce JC, Papermaster BW.

The role of the thymus in development of immunologic capacity in rabbits and mice.

J Exp Med 1962; 116:733-96

8

Archer OK, Pierce JD.

Role of the thymus in development of the immune response.
Fed. Proc. 20:26, 1961.
AAI/FASEB Spring 1961, Atlantic City, New Jersey

9
Martinez C, Kersey J, Papermaster BW, Good RA.
Skin homograft survival in thymectomized mice.
Proc. Soc. Exp. Biol. Med; 109, 193, 1962

10
Miller JFAP. Immunological function of the thymus.
Lancet 2:748. 1961a

11
Maclean LD, Zak SJ, Varco RL, **Good RA.**
The role of the thymus in antibody production; an experimental study of the immune response in thymectomized rabbits.
Transplant Bull 1957; 4:21-22

12
Good RA, Zak SJ.
Disturbances in gamma globulin synthesis as “experiments of nature”,
Pediatrics, 18:109, 1956

13
Good RA. Agammaglobulinemia-a provocative experiment of nature.
Bull. Univ. Minn. Hosp. Minn. Med. Found. 26:1, 1-19, 1954a

14
Good RA, Campbell B.
Potentiating effect of anaphylactic and histamine shock upon Herpes simplex virus infection in rabbits.
Proceedings of the Society for Experimental Biology & Medicine 59:305-306, 1945

15
Good RA.
Absence of plasma cells from bone marrow and lymph nodes following antigenic stimulation in patients with agammaglobulinemia.
Revue d’Hematol., 9:502, 1954 b

16
Good RA, Varco RL.
A clinical and experimental study of agammaglobulinemia.
J. Lancet: 75;245, 1955a

17

MacLean LD, Zal SJ, Varco RL , **Good RA.**
Thymic tumor and acquired agammaglobulinemia: a clinical and experimental study of the immune response.

Surgery; 40:1010, 1956

18

Boyd E.

Growth of the thymus: Its relation to status thymicolymphaticus and thymic symptoms.

AMA, Am. J. Dis. Child; 33:867, 1927

19

Boyd E.

The weight of the thymus gland in health and disease.

AMA., Am. J. Dis. Child; 43:1162, 1932

20

Scammom RE.

The prenatal growth of the human thymus.

Proc. Soc. Exper. Biol. & Med; 24:906, 1927

21

Scammon RE.

Developmental anatomy, in Morris' Human Anatomy, Ed., 11, Schaeffer, J.P., Ed., McGraw-Hill, New York, 1953, p.1.

22

MacLean LD, Zak SJ, Varco RL, **Good RA.**

Thymic tumor and acquired agammaglobulinemia: a clinical and experimental study of the immune response.

Surgery; 40:1010, 1956

23

Good RA, Varco RL

A successful homograft of skin in a child with agammaglobulinemia: studies on agammaglobulinemia

J Am. Med. Assoc., 147: 713, 1959

24

MacLean LD, Zak SJ, Varco RL, **Good RA**

The role of the thymus in antibody production: an experimental study of the immune response in thymectomized rabbits

Transplant. Bull. 4:21, 1957

25

Archer OK, Pierce JC, Papermaster BW, **Good RA.**

Reduced antibody response in thymectomized rabbits.

Nature; 191,192, 1962

26

Papermaster BW, **Good RA.**

Relative contributions of the thymus and the bursa of Fabricius to the maturation of the lymphoreticular system and immunological potential in the chicken

Nature 196, 836, 1962

27

Papermaster BW, Dalmaso AP, Martinez C , **Good RA.**

Suppression of antibody forming capacity with thymectomy in the mouse.

Proc. Soc. Exp. Biol. Med, 111, 41, 1962

28

Dalmaso AP, Martinez C, **Good RA.**

Further studies of suppression of the homograft reaction by thymectomy in the mouse

Proc. Soc. Exp. Biol. Med. 110, 205, 1962a

29

Good RA, Dalmaso AP, Martinez C, Archer OK, Pierce JC, Papermaster BW

The role of the thymus in the development of immunologic capacity in rabbits and mice

J. Exp. Med. 116, 773, 1962

30

Papermaster BW, Friedman DI, Good RA

Relationship of the bursa of Fabricius to immunologic responsiveness and homograft immunity in the chicken

Proc. Soc. Exp. Biol. Med. 110, 62, 1962

31

Martinez C, Dalmaso AP, **Good RA**

Acceptance of tumor homografts by thymectomized mice

Nature 194, 1289, 1962

32

Miller JFAP

Turning Points in Modern Immunology:

The discovery of thymus function and of thymus derived lymphocytes

Immunological Reviews Vol 185 July 2002

33

Good RA, Campbell B

Potentiating effect of anaphylactic and histamine shock upon Herpes simplex virus infection in rabbits

Proc. Soc. Exp. Biol. Med. 59:305-306, 1945

34

Bruton OC

Agammaglobulinemia

Pediatrics 9, 722-728, 1952

35

Mazzitello WF, **Good RA**

The clinical problem of agammaglobulinemia

Postgrad. Med. 20, 95, 1956

36

Good RA, et al.

Unpublished discussion,

Annual meeting of the American Association of Immunologists, Atlantic City, New Jersey, April 1961

37

Miller, JFAP

Ch. 10 Immunological Function of the Thymus and Thymus-Derived Cells

In: The Immunologic Revolution: Facts and Witnesses

Edited by Andor Szentivanyi and Herman Friedman

38

Martinez C, Kersey J, Papermaster BW, **Good RA**

Skin homograft survival in thymectomized rabbits

Nature 191,191,1962

39

Dalmasso AP, Martinez C, **Good RA**

Failure of spleen cells from thymectomized mice to induce graft vs host reactions

Proc. Soc. Exp. Biol. Med 111,143,1962b

40

Papermaster BW, Bradley SG, Watson DW, **Good RA**

Antibody-producing capacity of adult chicken spleen cells in newly hatched chicks: A study of sources of variation in a homologous cell transfer system

J. Exp. Med. 115, 1191, 1962

41

Glick B, Chang TS, Jaap RG

The bursa of Fabricius and antibody production

Poultry Science, 35, 224, 1956

42

Miller, J

Turning Points in Modern Immunology-The discovery of thymus function and of thymus derived lymphocytes

Immunologic Reviews, Vol. 185, July 2002

43

Fenner F

Interview for the 1999 Australian Academy of Science's 100 Years of Australian Science Interviews with Australian Scientists

Professor Jacques Miller, pathologist

1999

44

Dalmaso AP, Martinez C, Good RA

Failure of spleen cells from thymectomized mice to induce GVHR

Proc. Soc. 110:205-208, 1962

45

Good RA, Dalmaso AP, Martinez C, Archer OK, Pierce JC, Papermaster BW

The role of the thymus in development of immunologic capacity in rabbits and mice

J. Exp. Med. 116:773-796, November, 1962

46

Miller, JFAP Analysis of the thymus influence in leukaemogenesis

Nature, September 1961, 191: 248-249

**The reader is encouraged to read Chapter 9 ; *The Minnesota Scene: A Crucial Portal of Entry to Modern Cellular Immunology* by Robert A. Good ,in the book, The Immunologica Revolution:Facts and Witnesses for Good's own perspective of the discovery of the role of the thymus in mammalian immunity. For more information on Dr. Good and his accomplishments, c.v. and bibliography please visit his website at www.RobertAGoodArchives.com .