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FINAL REPORT

THE ECOLOGY OF THE INTESTINAL FLORA IN A CHANGING ENVIRONMENT

NASA Contract NAS9-10765

February 8, 1971

Submitted by: T. D. Luckey
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Introduction

The effect of isolation upon the intestinal microflora was reviewed in 1963 (Engley) and brought to the attention of NASA as a potential hazard in 1964 (Luckey) at the Tampa Conference on Nutrition in Space and Related Waste Problems. This concept was reinforced by Gustafsson (1965) who said "The two most hazardous things an astronaut takes into his capsule in an extended flight - - - are his brains and his intestinal flora..." (Human Ecology Space Flight Conference held at Princeton, New Jersey). Potential hazards on prolonged space flights were reviewed in the article Potential Microbic Shock in Manned Aerospace Systems (Luckey, 1966). These were placed in broader perspective in the article, Gnotobiology and Aerospace Systems (Luckey, 1968). The major concepts proposed have been verified in a variety of ways although it is obvious that the system is not simple and some controversy exists in the literature with different experiments. A recent review entitled The Effects of Bioisolation by Bengtson (1970) shows the work done to date. Such information makes it necessary to obtain all the information possible on the effect of environment upon the microflora. The tasks of defining the intestinal microflora, the permissible levels, interactions, function and role in vivo of different organisms of the intestinal microflora are important areas where knowledge must be accumulated in order that man may safely enter space missions of extended duration.

Persuant to the above problem it is important to have a series of conferences on the emerging concept of anaerobes as the predominant species (99%) of the intestinal flora of animals and man. The conferences would bring together experts in various areas of the anaerobic microflora of man to elucidate the problem and to discuss present knowledge about the role of these microorganisms in the host. With this goal a symposium was held March 30-31, 1970 at the University of Missouri, Columbia entitled, The Ecology of the Intestinal Flora in a Changing Environment.

The program is essentially that given in the Appendix A, the printed program for the meeting. Minor deviations included the fact that Drs. Rolf Freder and Russ Schaedler could not attend due to the combination of a severe snow storm and the air transportation strike during the days immediately preceding the conference. Drs. Dave Hentges and Frank Engley from the Department of Microbiology of this campus took those two

moderator positions respectively. The program in Appendix A was developed without participation of any of the Russians who have experience in this field because communication through the mail appeared to be difficult (see letters in Appendix B). It appeared that time was a major factor since the two answers seemed to be encouraging and personal communication with Dr. D. G. Kudlai at the Xth International Congress for Microbiology in Mexico last August suggested that the Russian scientists would be willing to get together if adequate arrangements could be made ahead of time.

Following the formal symposium, the speakers and selected members attending were invited to participate in a clinical discussion with Dr. John Spratt of the Ellis Fischel Hospital on April 1. Here were explored ways and means to control the intestinal microflora in cancer and post surgery patients. This meeting was surprisingly productive and satisfying to the participants. Some of the concepts and information were immediately used in a grant application to National Cancer Institute for money to study ways and means to ensure a benign intestinal microflora in patients. Dr. John Spratt, the director of Ellis Fischel Hospital would like to cooperate on future symposia (see Appendix C).

The proceedings of the symposium have been written and were published in the November issue of the American Journal of Clinical Nutrition, Vol 23, No. 11, pages 1429-1540, 1970. All participants were very cooperative in submitting their material for publication and in cooperating with the editors in modifying the material as requested. By arrangement with the director of the symposium a second part of the symposium entitled Bacterial and Intestine Function in Human Disease, which was published in the December issues of the same journal, was combined with our symposium proceedings and given an introduction. These were published as a book entitled "Intestinal Microflora". This is available for purchase at \$3.50 each from The American Journal of Clinical Nutrition, 9650 Rockville Pike, Bethesda, Maryland - 20014.

This was printed by the Williams and Wilkins Company of the Waverley Press, Inc., Mount Royle and Gilford Avenues, Baltimore, Maryland 21202. This booklet contains all the symposium articles presented in the November issue of The American Journal of Clinical Nutrition. It is appended to this final report. About 300 persons attended and over 1000 reprint requests have been received by the authors.

The symposium highlight for most was the presentation of Dr. Helmut Haenel entitled "Human Normal and Abnormal Gastrointestinal Flora". The expertise of Dr. W. T. Bryant in his presentation and discussions of the anaerobic flora were most helpful. The highlight for me was the presentation of Dr. D. C. Savage entitled "Associations of Indigenous Microorganisms with Gastrointestinal Mucosal Epithelia". This work shows how much we will have to learn in the future about the intimate relationships between the microflora and the intestinal mucosa of the host.

Notices of the symposium and a summary of the symposium were released to the local news media, AP and UP press, American Society for Microbiology News, Science, American Institute of Biological Sciences for Bioscience, American Institute of Nutrition News, Feedstuffs, Laboratory Management, Chemical and Engineering News, Scientific Research, Applied Microbiology, American Medical Association News, Journal of American Veterinary Association and Journal of Medical Association. These plus the present advertisement being given by the American Journal of Clinical Nutrition to the book entitled "Intestinal Microflora" has given this symposium good publicity. This symposium was designated as the Spring Meeting of the Missouri Branch of the American Society of Microbiology. This was done through the work of Dr. Joe Parisi, Department of Microbiology, on this campus. The symposium itself was well attended and there has been good reprint request from the publication of the articles in the November, 1970 issue of the American Journal of Clinical Nutrition. We anticipate good response to the publication of the book as soon as it is advertised.

Summary

The proceedings of the symposium entitled "Ecology of the Intestinal Flora in a Changing Environment" submitted for publication and published in the November 1970 issue of The American Journal of Clinical Nutrition, pages 1249-1540. The proceedings of this symposium was combined with a clinical section which was published in the December issue of the same journal entitled Bacteriology and Intestinal Function in Human Diseases. The combination was published as a book entitled "Intestinal Microflora" which is now available from The American Journal of Clinical Nutrition.

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Recommendations

The symposium underscored the complexity of the subject of the microflora and our ignorance of much of the activities of that microflora. It also indicated that the communication provided by such a meeting was invaluable in educating each other and the members of the audience as well as those who read the reports. This was particularly true in the case of anaerobic rumen workers who could contribute much of their suggestions and concepts to those working in the area of monogastric animals. This was also true of those innovative persons such as Dr. Savage who are exploring new techniques to investigate the intestinal microflora. The first recommendation is that more support should go to research in this area. The work with monoflora and defined flora animals, in a gnotobiotic system is just beginning; it will lead to a good concept of microbial interactions within and with the host. Finally, a second symposium should be held to further define the interactions, functions and the role of the intestinal microflora; to determine some of the permissible levels of specific elements of the flora; and what makes potential pathogens become pathogenic under different conditions. A tentative program for such a symposium is provided as Appendix C. This should be published. Finally, an American-Russian symposium should be held and the proceedings published in English and Russian editions on microbial problems and the state of the art knowledge of man in isolation. This should be held in the near future as a fitting termination of our Apollo Space Program. In this, and related fields such as nutrition, the work and information done should be recorded permanently before the knowledge is lost and the persons involved have changed.

References

- Bengson, M. H., 1970. Effects of bioisolation. *Am. J. Clin. Nutr.* 23:1525.
- Gustafsson, B., 1968. Intestinal microflora and germfree Life. In "Human Ecology in Space Flight", Ed. D.H. Calloway, Vol. 3, p. 119, New York Acad. Sci., New York.
- Luckey, T. D., 1963. "Germfree Life and Gnotobiology" Academic Press, Inc., New York.
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- Luckey, T. D., 1966. Potential microbial shock in manned aerospace systems. *Aerospace Med.* 37:1223.

Luckey, T. D., 1968. Gnotobiology and aerospace systems. In "Advances in Germfree Research and Gnotobiology, Ed. M. Miyakawa and T. D. Luckey, Chem. Rubber Co., Cleveland.

ECOLOGY OF THE INTESTINAL FLORA IN A CHANGING ENVIRONMENT

App. A

First International Symposium
Presented by:

The University of Missouri-Columbia School of Medicine and Extension Division with the cooperation of the School of Veterinary Medicine, The Space Sciences Research Center and the Graduate School and held in connection with the Spring meeting of the Missouri Branch of the American Society for Microbiology.

MEDICAL CENTER AUDITORIUM

Monday, March 30

MARCH 30-31, 1970

Tuesday, March 31

A.M.

- 8:15 Registration and Coffee
- 8:45 Welcome -- Dean Kingrey
- NORMAL FLORA
- Moderator -- Rolf Freter
- 8:50 Introduction -- Don Luckey
- 9:00 Human Normal and Abnormal Flora
Helmut Haenel
- 9:30 Fecal Flora of Man -- Lorraine Gall
- 9:50 Coffee Break
- 10:00 Pathogen-Normal Flora Interactions
Dave Hentges
- 10:20 Rumen Microbes -- Marv Bryant
- 10:50 Discussion
- *12:00 Lunch and Tour -- Space Sciences Research
Center -- John McKenna

P.M.

EFFECT OF ANTIBIOTICS AND DIET

Moderator -- Herb Goldberg

- 2:00 Effect of Antibiotic Therapy
Sydney Finegold
- 2:30 Ecologic Consequences of Resistance Transfer
Factors -- Sidney Cohen
- 3:00 Coffee Break
- 3:15 Antibiotics Influence Microflora and Drug
Resistance in Domestic Animals
Williams Smith
- 3:45 Human Fecal Flora Under Controlled Diet
Intake -- Stan Speck
- 4:05 Discussion

A.M.

- 8:50 Welcome -- Dean Bloomfield
- ACTIVITIES OF MICRO FLORA
- Moderator -- Russ Schaedler
- 9:00 Metazoa-Protozoa-Bacteria Interrelationships
Dick Wescott
- 9:20 Bacteria-Mucosa Interactions -- Dyane Savage
- 9:50 Coffee Break
- 10:10 Energy Metabolism in Anaerobes
Lee Baldwin
- 10:40 Metabolic Contributions of the Cecal Flora
Richard McBee
- 11:00 Discussion
- 12:00 Lunch (on your own)

P.M.

EFFECT OF ISOLATION

Moderator -- Jim McQueen

- 1:30 Changes During Hibernation -- Ella Barnes
- 2:00 Effect of Bioisolation -- Bang Bengson
- 2:20 Coffee Break
- 2:35 Gnotobiology as Ecology -- Don Luckey
- 2:50 Discussion
- 3:20 Summary and Perspective
Moderator -- Bill McCulloch with Rolf Freter,
Herb Goldberg, Russ Schaedler, Jim
McQueen, and Frank Engley

"May there never develop in me the notion that my education is complete but give me the strength and leisure and zeal continually to enlarge my knowledge".

--Maimonides

MONDAY EVENING

6:00 P.M. - RAMADA INN - Social Hour - Dinner Meeting
Welcome: Bob Schiffman - Collegium Musicum: Andy Minor
"Women in Space": Dick Lawton

Appendix B

Dr. T. D. Luckey
University of Missouri
Department of Biochemistry
M 121 Medical Science
Columbia, Mo. 65201
U. S. A.

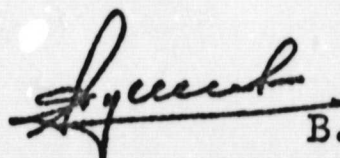
March 1, 1970

Dear Dr. Luckey:

We feel very thankful to you for your kind invitation to attend the International Symposium on The Ecology of the Intestinal Flora in a Changing Environment. Unfortunately, we received only your second letter which reached us with a long delay. Therefore, we were unable to send you the necessary information before the deadline expired.

We hope that we shall be able to get acquainted with the papers to be presented at the Symposium and thank you in advance for your assistance in this field.

Sincerely yours,



B. Adamovich

BA:gt

Москва, В-312, ул. Вавилова, 32

Комиссия по исследованию и использованию
космического пространства АН СССР

Профессор ВИКТОР МИХАИЛОВИЧ ЖДАНОВ

Действительный член Академии медицинских наук СССР

Институт вирусологии имени Д. И. Ивановского

Москва, Д-98, 1-й Шукшинский проезд, 24.

Тел. Д 4-52-50.

Dr. T. D. Lucky, Ph.D.
University of Missouri-Columbia
M121 Medical Science
Columbia, Mo. 65201

April 21, 1970

Dear Dr. Lucky:

Thank you for your letter of March 5, 1970 and information about the International Symposium entitled; "Ecology of the Intestinal Flora in a Changing Environment".

Since I am not engaged in this field I applied to the authorities of the USSR Ministry of Public Health, but there was too little time for arranging all formalities. If in future you possess some information of interesting International gatherings please forward it in good time to the External Relationships Dept. of the USSR Academy of Medical Sciences or to that of the USSR Ministry of Public Health.

Sincerely yours,

V. Zhdanov

Prof. V. Zhdanov

App. C

Tentative Program*

Second International Symposium
on Intestinal Microecology

1st Day

- 8:15 Welcome - Chancellor, University of Missouri, Columbia.
THE INDIGENOUS GASTRO-INTESTINAL FLORA.
- 8:20 EPITHELIAL ASSOCIATIONS OF THE INDIGENOUS FLORA.
D. C. Savage, University of Texas, Austin
- 8:50 GASTRO-INTESTINAL FLORA ONTOGENY IN CHILDREN OF A NON-INDUSTRIAL SOCIETY.
L. J. Mata, Guatemala
- 9:20 THE INDIGENOUS INTESTINAL FLORA OF ADULTS.
B. S. Drasar, England
- 9:50 Coffee
- 10:05 ANAEROBES IN THE HUMAN INTESTINE.
S. M. Finegold - Los Angeles
- 10:30 INTESTINAL MICROBES IN RUMINANTS.
R. E. Hungate, University California, Davis
- 11:00 Discussion
INTERACTIONS AMONG INTESTINAL BACTERIA IN GNOTOBIOLOGY
- 1:00 MICROFLORA INTERACTIONS IN THE RAT.
P. Raibaud, Paris, France
- 1:30 ENTERIC BACTERIA INTERACTIONS IN INVERTEBRATES.
B. Greenberg
- 2:00 SALMONELLA CONTROL BY SPECIFIC MICROBES
S. Sasaki, Tokyo, Japan
- 2:30 SHIGELLA - COLI INTERACTIONS IN MICE
B. R. Maier and D. Hentges, University of Missouri, Columbia
- 3:00 Coffee
- 3:15 INTESTINAL FLORA IN CHOLERA
S. L. Gorbach, University of Illinois
- 3:45 Discussion

*None of the speakers have been contacted; therefore, this must be considered to be a representative program.

2nd Day

HOST-NORMAL FLORA INTERACTIONS

- 8:20 Welcome, Dean Graduate School
- 8:30 CONTRIBUTIONS OF THE ALIMENTARY TRACT FLORA TO HOST NUTRITION
J. R. Pleasants, University of Notre Dame
- 9:00 IMPORTANCE OF ENTERIC BACTERIA ON INTESTINAL PARAMETERS
S. Syed, University of Michigan
- 9:30 NORMAL FLORA AND INTESTINAL MOTILITY
G. D. Abrams, University of Michigan
- 10:00 Coffee
- 10:15 BACTERIA, FIBER AND OTHER FACTORS AFFECTING CECAL SIZE IN
GNOTOBIOTIC RODENTS
T. D. Luckey, University of Missouri, Columbia
- 10:45 ONTOGENY OF THE IMMUNE RESPONSE IN GERMFREE PIGLETS
Y. B. Kim, University of Minnesota
- 11:15 Discussion

HOST-PATHOGEN INTERACTIONS

- 1:00 MECHANISMS OF SHIGELLA PATHOGENESIS
S. B. Formal, Walter Reed Hospital
- 1:30 E. COLI TOXIGENISES IN ANIMALS
H. W. Moon, Ames Research Lab.
- 2:00 INTESTINAL FLORA AND NON SPECIFIC DIARRHEA
U. Utrecht
- 2:30 PATHOGENESIS OF SALMONELLA
H. Sprintz, H. Scheider
- 3:00 Coffee
- 3:15 MECHANISMS OF CHOLERA PATHOGENICITY
R. A. Finklestein, Southwestern University, Dallas, Texas
- 3:45 Discussion
- 4:15 PERSPECTIVES
F. S. Cheever, University of Pittsburg

3rd Day

IDENTIFICATION OF INTESTINAL ANAEROBE

8:30-10:00

WORKSHOP FOR ANAEROBE IDENTIFICATION

W. E. C. Moore, University of West Virginia

10:00

Coffee

10:15

WORKSHOP IN GAS CHROMATOGRAPHY

C. W. Gehrke, University of Missouri, Columbia

P.M.

Begin 2 day Gas Liquid Chromatography Basic Short Course for any interested persons. This would cover GLC including basic principles, experimental design, limitations, applications and to practice.

8:30

NEED FOR CLINICAL CONTROL OF THE INTESTINAL FLORA

J. Spratt, Ellis Fischel Hospital, Columbia

9:00

Discussion