FINAL REPORT

NOVEMBER 1982 - JULY 1987

NASA Agreement no. NCC2-213

"DEVELOPMENT AND TESTING OF A MOUSE SIMULATED SPACE FLIGHT MODEL"

Gerald Sonnenfeld, Ph.D., Principal Investigator*

Department of Microbiology and Immunology
School of Medicine
University of Louisville
Louisville, KY 40292

*The NASA technical officer for this agreement is: Dr. Adrian D. Mandel
Mail Stop 239-7
NASA Ames Research Center
Moffett Field, CA 94035

(NASA-CR-181155) DEVELOPMENT AND TESTING OF A MOUSE SIMULATED SPACE FLIGHT MODEL Final Report, Nov. 1982 - Jul. 1987 (Louisville Univ.) 11 p Avail: NTIS HC A02/MF A01 CSCL 06B G3/51

N87-25708

Unclas
0084705

INTRODUCTION

We have recently completed this project concerning the development and testing of a mouse model for simulating some aspects of weightlessness that occurs during space flight, and the carrying out of immunological experiments on animals undergoing space flight. The mouse model we have developed was an antiorthostatic, hypokinetic, hypodynamic suspension model similar to the one used with rats [1-3].

Our subsequent studies were divided into two parts. The first involved determination of which immunological parameters should be observed on animals flown during space flight or studied in the suspension model. The second involved suspending mice and determining which of those immunological parameters were altered by the suspension. In addition, we were fortunate to be able to test our hypotheses using rats that were actually flown in Space Shuttle SL-3.

We believe the studies carried out during this project were highly successful. They have yielded much insight to allow for planning of future immunological experiments for space flight in the Space Shuttle and, possibly, for Space Station.

METHODS, RESULTS AND DISCUSSION

Our first studies involved the development of a murine antiorthostatic suspension model [3]. This model was similar to the model developed for rats [1,2]. Similar effects of antiorthostatic suspension on muscle, bone, electrolyte levels and urine and feces output were observed using the mouse model as were observed using the established rat model [3].

We next began studies to determine which immunological parameters were most important to study. We chose interferons because of their significant activities as immunoregulators [4]. We were able to show that interferons could affect the course of a wide variety of infections, including protozoan [5-9] and bacterial [10-12] infections. Therefore, we established that interferons played a major role in regulating resistance to a wide variety of infections, and were worthy of study in animals exposed to space flight.

Our next phase of work was to use the mouse antiorthostatic suspension model to determine its effects on interferon production. Mice suspended for one or two weeks in the model showed inhibited interferon production [13]. The inhibition of interferon induction was transient, as suspended mice returned to normal caging for one week had restored interferon production. Orthostatically suspended control mice had normal interferon production, suggesting that more than just the stress of suspension was responsible for the inhibition of interferon induction observed in antiorthostatically suspended mice [13].

Additonal studies were carried out to determine how antiorthostatic suspension affected resistance to an infection. Female Swiss mice are normally completely resistant to infection with the D variant of

encephalomyocarditis virus (EMC-D virus) [14]. Mice that were suspended antiorthostatically became susceptible to infection [14], while orthostatically suspended control mice remained resistant. Loss of resistance to this interferon-sensitive virus correlated with the drop in interferon production.

Finally, we were able to use rats that had been flown in Space Shuttle SL-3. Spleens were removed from these rats and exposed to concanavalin-A [15]. Culture supernatant fluids were harvested and assayed for interferon-gamma and interleukin-3, another immunoregulatory substance. Interferon-gamma production was severely inhibited in flown rats, but interleukin-3 production was normal [15]. This suggests that there may be specific immunosuppressive effects of space flight.

All of these results suggest that further studies are warrented to determine the effects of space flight on immune responses. In addition, studies on the significance of these effects to host health needs to be determined.

PUBLICATIONS

The following are publications relating to this project and acknowledeging support of NASA award NCC2-213. Copies of all published articles are appended to this report. Copies of articles in press, submitted and in preparation will be forwarded as a supplement to this report when they are available.

1. Kumar, V., Lust, J., Gifaldi, A., Bennett, M., and Sonnenfeld, G. Lack of correlation between mycoplasma induced interferon-gamma production in vitro and natural killer cell activity against FLD-3 cells. Immunobiology, 165:445, 1983.
2. Kierszenbaum, F., and Sonnenfeld, G. Beta-interferon inhibits cell infection by Trypanosoma cruzi. J. Immunol. 132:905, 1984.
3. Biron, C.A., Sonnenfeld, G., and Welsh, R.M. Interferon induces natural killer cell blastogenesis in vivo. J. Leukocyte Biol. 35:31, 1984.
4. Sonnenfeld, G. Contradictory results in interferon research. Survey Immunol. Res. 3:198, 1984.
5. Steffen, J.M., Robb, R., Dombrowski, M.J., Musacchia, X.J., Mandel, A.D., and Sonnenfeld, G. A suspension model for hypokinetic/hypodynamic and antiorthostatic responses in the mouse. Aviat. Space Environ. Med. 55:612, 1984.
6. Rollag, H., Degre, M., and Sonnenfeld, G. Effects of interferon-alpha/beta and interferon-gamma on phagocytosis by mouse peritoneal macrophages. Scand. J. Immunol. 20:149, 1984.
7. Sonnenfeld, G. Effects of interferon on antibody formation. In:

Interferons and the Immune System, J. Vilcek and E. DeMaeyer, eds., Elsevier Scientific publishers, Amsterdam, p. 85, 1984.

8. Rose, A.M., Steffen, J.M., Musacchia, X.J., Mandel, A.D., and Sonnenfeld, G. Effect of antiorthostatic suspension on interferon-alpha/beta production by the mouse. Proc. Soc. Exp. Biol. Med. 177:253, 1984.
9. DeGee, A.L.W., Sonnenfeld, G., and Mansfield, J.M. Genetics of resistance to the African trypanosomes. V. Qualitative and Quantitative differences in interferon production among susceptible and resistant mouse strains. J. Immunol. 134:2723, 1985.
10. Sonnenfeld, G., DeGee, A.L.W., Mansfield, J.M., Newsome, A.L., Arnold, R.R., and Kierszenbaum, F. Role of interferon in resistance and immunity to protozoa. In: The Biology of the Interferon System, 1984, H. Kirchner and H. Schellekens, eds., Elsevier Science Publishers, B.V., Amsterdam, p. 299, 1985.
11. Wirth, J.J., Kierszenbaum, F., Sonnenfeld, G., and Zlotnik, A. Enhancing effects of gamma interferon on phagocytic cell association with and killing of Trypanosoma cruzi. Infect. Immun. 49:61, 1985.
12. Sonnenfeld, G. The natural immunoregulatory role of interferon. Ann. Institut Pasteur 136D:77, 1985.
13. Sonnenfeld, G., Wirth, J., Kierszenbaum, F., DeGee, A.L.W., and Mansfield, J.M. Interferon effects on protozoan infections. In: The Interferon System, F. Dianzani and G.B. Rossi,eds., Serono Symposia Volume 24, Raven Press, New York, p. 195, 1985.
14. Gould, C.L., Williams, J.A., Mandel, A.D., and Sonnenfeld, G. Effect of flight in mission SL-3 on interferon-gamma production by rats. The

Physiologist, 28:S213, 1985.

15. Sonnenfeld, G., Gould, C.L., Kierszenbaum, F., DeGee, A.L.W., and Mansfield, J.M. Interferon in resistance to bacterial and protozoan infections. In: The Biology of the Interferon System, 1985, W.E. Stewart II and H. Schellekens, eds., Elsevier Science Publishers, B.V. Amsterdam, p. 291, 1986.
16. Gould, C.L., Degee, A.L.W., Mansfield, J.M., and Sonnenfeld, G. Trypanosma brucei rhodesiense infection prevents virus-induced diabetes: Possible role of interferon and immunological mechansisms. J. Interferon Res. 6:499, 1986.
17. Deepe, G.S., Jr., Smith, J.G., Sonnenfeld, G., Denman, D., and Bullock, W.E. Development and characterization of Histoplama capsulatum reactive murine T-cell lines and clones. Infect. Immun. 54:714, 1986.
18. DeGee, A.L.W., Mansfield, J.M., and Sonnenfeld, G. Treatment of trypanosome-infected mice with exogenous interferon, interferon inducers or antibody to interferon. J. Parasitol. 42:792, 1986.
19. Gould, C.L., and Sonnenfeld, G. Enhancement of viral pathogenesis in mice maintained in an antiorthostatic suspension model: coordination with effects on interferon production. J. Biolog. Regult. Homeostat. Agents. 1:36, 1987.
20. Baral-Netto, M., Reed, S.G., Sadigursky, M., and Sonnenfeld, G. Specific immuniztion of mice against Leishmania mexicana amazonensis using solubilized promastigotes. Clin. Exp. Imunol. 67:11, 1987.
21. Gould, C.L., and Sonnenfeld, G. Effect of treatment with interferon-gamma and concanavalin-A on the course of infection of mice with Salmonella typhimurium strain LT-2. J. Interferon Res. 7:255,

1987.

22. Klein, J.B., McLeish, K.R., Sonnenfeld, G., and Dean, W.L. Potential mechanisms of cytostolic calcium modulation in interferon-gamma treated U-937 cells. Biochem. Biophys. Res. Commun. 145:1295, 1987.
23. Gould, C.L., Lyte, M., Williams, J.A., Mandel, A.D., and Sonnenfeld, G. Inhibited interferon-gamma but normal interleukin-3 production by spleen cells from rats expsoed to spaceflight conditions. Aviat. Space Environ Med., In Press, 1987.
24. Sonnenfeld, G., Kierszenbaum, F., Gould, C.L., DeGee, A.L.W., and Mansfield, J.M. Interferons and protozoan infections. In: The Interferon System: A Current Review, S. Baron, F. Dianzani, G.J. Stanton, and W.R. Fleischmann, Jr., eds. University of Texas Press, Austin, 1987.
25. Sonnenfeld, G. The promise of interferon therapy for parasitic diseases. In: Clinical Aspects of Interferon, M. Revel, ed., Martinus Nijhoff Publishing, Boston, In Press, 1987.
26. Sonnenfeld, G., and Kierszenbaum, F. Modulatory effects of interferons on Trypansoma cruzi infections. In: Interferon, Immunity and Intracellular Pathogens, G. Byrne and J. Turco, eds., Marcel Dekker, New York, In Press, 1987.
27. Sonnenfeld, G., Gould, C.L., Williams, J.A., and Mandel, A.D. Inhibited interferon production after space flight. Acta Microbiologica Hungarica, In Press, 1987.
28. Gould, C.L., DeGee, A.L.W., Smith, C.J., Mansfield, J.M., and Sonnenfeld, G. Studies on the mechanism of the inhibition of viral pathogenesis in mice infected with Trypanosoma brucei rhodesiense.

Submitted for publication, 1987.

29. Hershman, M.J., Polk, H.C., Jr., Pietsch, J.D., Kuftinec, D., and Sonnenfeld, G. Modulation of Klebsiella pneumoniae infection of mice by interferon-gamma. Submitted for publication, 1987.

30. Hershman, M.J., Sonnenfeld, G., Mays, B.W., Fleming, F., Trachtenberg, L.S., and Polk, H.C., Jr. Effects of interferon-gamma treatment on a surgically simulated wound infection of mice. Manuscript in preparation, 1987.

31. Hershman, M.J., Polk, H.C., Jr., Pietsch, J.P., Wellhausen, S.R., and Sonnenfeld, G. Modulation of infection following trauma by interferon-gamma treatment. Manuscript in preparation, 1987.

LITERATURE CITED

1. Deavers, D.R., Musacchia, X.J., and Meininger, G.A. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol., 49:516, 1980.
2. Morey-Holton, E., and Wronski, T.J. The Physiologist, 24:545, 1981.
3. Steffen, J.M., Robb, R., Dombrowski, M.J., Musacchia, X.J., Mandel, A.D., and Sonnenfeld, G. Aviat. Space Environ. Med., 55:612, 1984.
4. DeMaeyer, E. IN: Interferons and the immune system, J. Vilcek and E. DeMaeyer, eds. Elsevier Science Publishers, B.V. Amsterdam, p. 1, 1984.
5. Kierszenbaum, F., and Sonnenfeld, G. J. Immunol. 132:905, 1984.
6. DeGee, A.L.W., Sonnenfeld, G., and Mansfield, J.M. J. Immunol. 134:2723.
7. Wirth, J.J., Kierszenbaum, F., Sonnenfeld, G., and Zlotnik, A. Infect. Immun. 49:61, 1985.
8. Gould, C.L., DeGee, A.L.W., Mansfield, J.M., and Sonnenfeld, G. J. Interferon Res. 6:499, 1986.
9. DeGee, A.L.W., Mansfield, J.M., and Sonnenfeld, G. J. parasitol. 42:792, 1986.
10. Rollag, H., Degre, M., and Sonnenfeld, G. Scand. J. Immunol. 20:149, 1984.
11. Gould, C.L., and Sonnenfeld, G. J. Interferon Res. 7:255, 1987.
12. Klein, J.B., McLiesh, K.R., Sonnenfeld, G., and Dean, W.L. Biochem. Biophys. Res. Commun. 145:1295, 1987.
13. Rose, A.M., Steffen, J.M., Musacchia, X.J., Mandel, A.D., and Sonnenfeld, G. Proc. Soc. Exp. Biol. Med. 177:253, 1984.
14. Gould, C.L., and Sonnenfeld, G. J. Biolog. Regulat. Homeostat. Mech.

1:36, 1987.

15. Gould, C.L., Lyte, M., Williams, J.A., Mandel, A.D., and Sonnenfeld, G. Aviat. Space Environ. med., In Press, 1987.