MINUTES

TEXAS BOARD OF CORRECTIONS

350th Meeting

September 13, 1976

Dallas Hilton Hotel

Dallas, Texas

APPENDIX B

1. Title of Research Proposal: The Effect of Dietary Fat on the Fractional Catabolic Clearance of Low Density Lipoproteins in Normal Subjects.

2. Principal Investigator and associates: Principal Investigator, O. David Taunton, M.D.; Associates, Daniel Yeshurun, M.D.; Ramon Segura, M.D.; Antonio M. Gotto, Jr., M.D.

3. Departments Involved: Department of Medicine

4. Other Research Support: Lipid Research Clinic Contract #NIH 71-2156

5. Duration of Study: 8½ weeks

6. No. of Subjects to be Hospitalized: 10

7. Duration of Occupancy of GCRC Bed by Each Subject: 8½ weeks

8. Maximum No. of Patients to be Hospitalized at One Time: 5

9. Background Information: The fatty acid composition of lipoproteins is dependent upon the diet and can be altered in 10-14 days by altering the type of fat ingested (Spritz, N. and Miskkel, M.A.: J. Clin. Invest. 48:78-86, 1969). The metabolic clearance of the lipoproteins may also be altered by diet since it is known that diets high in polyunsaturated fatty acids cause a lowering of plasma cholesterol compared to diets high in saturated fatty acids (Ahrens, E. H., Jr., Blankenhorn, D. and Peterson, M.C. Lancet 1:943, 1957). Recent studies in this laboratory have shown that an infusion of intralipid, which is a fat emulsion consisting of soybean triglyceride, egg lecithin and glycerol, causes a decrease in the fractional catabolic clearance of LDL. Intragastric infusion of the intralipid had no effect upon the fractional catabolic clearance of LDL. Analysis of the fatty acid composition of phospholipids in the low density lipoproteins following the intralipid showed an increase in the saturated fatty acid content compared to the LDL phospholipids prior to the injection. It has therefore been postulated that the phospholipid composition of the low density lipoproteins influences the rate of catabolism of the LDL. We wish to extend these studies by a more physiologic approach. In this study we will investigate the effect of altering the composition of phospholipids by dietary means and determine the effect of this alteration on the rate of catabolism of LDL.

10. Purpose of Project: The purpose of this study is to determine the effect of dietary fatty acids on the fractional catabolic clearance of the low density lipoproteins in normal subjects and correlate this information with changes in the lipid composition of the LDL.

11. Uniqueness of the Project and Probability of Publishable Results: This study should result in new information regarding low density lipoprotein catabolism which will be suitable for publication.

12. Description of Study: Ten prisoner volunteers will participate in the study. Five volunteers will be admitted at a time.

Description of Diets: Isocaloric diets containing 40% of calories as fat, 40% as carbohydrate and 20% as protein to maintain body weight will be used. Diet 1 will be high in saturated fat and will have a P/S ratio of 0.25. Diet 2 will have a P/S ratio of 4. Each of the diets will contain approximately 400 mg. of cholesterol daily.

After being on diet 1 for 14 days, 100 mls. of blood will be collected from each subject in EDTA. The red cells will be removed by centrifugation. The LDL fraction will be isolated at d 1.025-1.050 by ultracentrifugation. The purity of the low density lipoproteins will be evaluated by immunochemical techniques. A portion of the LDL will then be analyzed for lipid composition including cholesterol, cholesterol ester, triglycerides and phospholipids. The fatty acid composition of the cholesterol ester, triglyceride and phospholipid fractions will then be determined by gas liquid chromatography. A portion of the LDL will then be labelled with I^{125} by the iodine monochloride technique. The free iodide will then be dialyzed from the LDL. The percent iodine in the LDL apoprotein will then be determined by extracting the lipid with chloroform/methanol and determining the percentage of counts in the lipid fraction. 25 µCi of I^{125} labelled LDL will then be injected through a millipore filter and blood samples obtained at various time intervals to determine the clearance of the labelled LDL as previously described (Langer, T., Strober, W. and Levy, R. I. J. Clin. Invest. 51:1528, 1972). The disappearance of the I^{125} LDL will then be followed for 14 days. Urine will be collected and the excretion of the I^{125} monitored. One gram of potassium iodide solution will be given daily to prevent thyroid uptake of the I^{125}. The subjects will then be placed on the second diet and the above studies repeated.

With the second group of 5 subjects the sequence of the diets will be reversed so that diet 2 will be given first and diet 1 will follow.

13. Selection of Patients: Ten prisoner volunteers who agree to participate will be studied. Their plasma lipids and lipoproteins will be documented to be normal before studies are carried out.

14. Discomfort to Subjects: The only discomfort to subjects will be the venipuncture which is necessary to obtain the blood and to inject the labelled LDL.

15. Potential Hazards to Subjects and Safeguards for Same: There will be small radiation exposure associated with the injection of the 50 µCi of I^{125} LDL. The estimated total exposure from 50 µCi of I^{125} to a 70 kg subject is 0.092 rad.

16. Method of Obtaining Informed Consent of Human Subjects and Copy of Consent Form: Approval for the study will be obtained from the Committee on Research Involving Human Beings at the Methodist Hospital and Baylor College of Medicine as well as the Radioisotope Committee of The Methodist Hospital. A copy of the consent form is attached.

17. Possible Excessive Expense Associated with Study: None

BAYLOR COLLEGE OF MEDICINE
TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

WEBB MEDICINE DEPARTMENT OF SURGERY
(713) 529-4951

May 1, 1974

O. David Taunton, M. D.
Department of Medicine
Baylor College of Medicine
Houston, Texas 77025

Dear Dr. Taunton:

The Baylor Committee on Research Involving Human Beings is pleased to inform you that your research proposal The Effect of Dietary Fat on the Fractional Catabolic Clearance of Low Density Lipoproteins in Normal Subjects (GCRC)

was approved on April 30, 1974 according to institutional guidelines and provided it receives the unaltered approval of the institutional committee in which it is involved.

1. Continued review will be required
   - ( ) a. After each subject's exposure
   - ( ) b. Quarterly
   - ( ) c. Semi-annually
   - (x) d. Annually
   - (x) e. Change in Protocol
   - (x) f. Development of unexpected problems or unusual complications
   - ( ) g. Other -

2. Method of Review
   - (x) a. Questionnaire (example enclosed)
   - ( ) b. New Protocol
   - ( ) c. Interview with principal investigator
   - ( ) d. Other

Sincerely yours,

E. Stanley Crawford, M. D.,
Chairman, Committee on Research
Involving Human Beings

ESC:lb

18. Signatures:

O. David Taunton, M.D.

O. David Taunton, M.D.
Principal Investigator

Henry D. McIntosh, M. D., Chairman
Department of Medicine

PATIENT CONSENT FORM

DETERMINATION OF INFLUENCE OF DIFFERENT TYPES OF DIETARY FAT ON LOW DENSITY LIPOPROTEIN CATABOLISM

I understand that physicians at Baylor College of Medicine and The Methodist Hospital are engaged in research and the study of the nature of disease and of new methods of diagnosis and treatment. I understand that Federal Law requires that a patient who is given an investigational drug should signify his willingness to receive it, after being told its nature and purpose. I understand that this investigation entails the radioactive labelling of one of the lipid-carrying proteins in my blood, which will then be sterilized and re-injected into my circulation (as I^{125}-low density lipoprotein). I have been informed that the total dose of radioactivity involved (50-100 micro curies of I^{125}) is not thought to be harmful in the light of present scientific knowledge and I agree to undergo this procedure, whose objective is to determine the influence of different types of dietary fat on the rate of clearance of low density lipoproteins from my plasma. I understand that the purpose of these procedures is to develop improved understanding and better methods of diagnosis and treatment of lipid transport disorders, but that at the present time no representation can be made that my participation will be directly beneficial to me.

There are no convenient alternative procedures, other than the ones described to me, by which this study could be carried out.

I have been offered the opportunity for further discussion with my physician and have been given the opportunity to ask any questions now or at a future time concerning the procedures to be carried out.

I understand that I am free to withdraw from this study at any time. I voluntarily consent to participation in this study with an understanding of the known effects that occur in the course thereof, and further understand that not all effects of these procedures are necessarily known at the present time.

Patient Name _____ Date _____

Patient Signature _____ Witness _____

Patient Number _____

BAYLOR COLLEGE OF MEDICINE
TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

THE MADING DEPARTMENT OF SURGERY
(713) 529-4951

September 13, 1972

Robert B. Couch, M.D.
Department of Microbiology
Baylor College of Medicine
Houston, Texas 77025

Dear Dr. Couch :

The Baylor Committee on Research Involving Human Beings is pleased to inform you that your research proposal Development of a Reproducible and Effective Challenge System for Mycoplasma pneumoniae, USPHS General Clinical Research Center RR 00350, USPHS Contract #PH-43-68-963, The Methodist Hospital Clinical Research Center, Ramsey Unit of the Texas Department of Correction was approved on September 12, 1972 according to institutional guidelines with the following provisions:

1. Continued review will be required
   - ( ) a. After each subject's experience
   - ( ) b. Quarterly
   - (.) c. Semi-annually
   - (x) d. Annually
   - (x) e. Change in Protocol
   - (x) f. Development of unexpected problems or unusual complications
   - ( ) g. Other

2. Method of Review
   - (x) a. Questionnaire (example enclosed)
   - ( ) b. New Protocol
   - ( ) c. Interview with principal investigator
   - ( ) d. Other

Sincerely yours,

E. Stanley Crawford, M.D.,
Chairman, Committee on Research
Involving Human Beings

ESC:ib

Title: Development of a Reproducible and Effective Challenge System for Mycoplasma pneumoniae

Principal Investigator and Associates: Robert B. Couch, M. D.
Vernon Knight, M. D.
Stephen Greenberg, M. D.
Julius A. Kasel, Ph. D.

Department Involved: Microbiology

Granting Agency: USPHS General Clinical Research Center RR 00350
USPHS Contract #PH-43-68-963

Duration of Support: 10/1/66 to 10/1/76
12/19/71 to 12/19/72

Location: The Methodist Hospital Clinical Research Center
Ramsey Unit of the Texas Department of Corrections

Outline:

Background Information: Considerable experience is available (a substantial proportion by us) with challenge of normal adult volunteers with Mycoplasma pneumoniae. This organism is an important cause of respiratory disease in all age groups and particularly of pneumonia in older children and young adults (see protocol entitled "Evaluation of Inactivated Vaccine for M. pneumoniae Infection").

In challenge of volunteers, 3 variables of the challange agent are involved; these are source and method of growth of the inoculum, inoculation method, and dose. Inocula used for challenge of volunteers have varied in propagation history; these include no propagation (natural throat secretions), tissue culture grown organisms, and various passage levels of organisms propagated on artificial media. Methods used for inoculations have included nasopharyngeal spray, nasal drops, and inhalation of small particle aerosol. Pneumonia has resulted from each inoculation method and with each source and method of growth of organisms.

The studies with varying levels of passage or organisms on artificial media suggested that propagation in artificial media resulted in loss of infectivity

and virulence for man. In fact, passage on artificial media has been used for possible development of attenuated vaccines. This suggests that disease producing capability is maintained with in vitro propagation only if the organism is grown in tissue cultures. The third variable of the challenge agent is dose administered. Only very high challenge doses (approximately 10^6 colony forming units (cfu)) have been used and the influence of dose is undetermined.

Despite this experience, no defined, reproducible challenge system is available for M. pneumoniae. If the results of studies in volunteers are to continue to be an important determining factor in new vaccine and therapeutic development then better defined methods for evaluation are needed. New vaccines are being developed which will require indications of effectiveness before proceeding to field trials. We believe before they are evaluated in volunteers the challenge system should be better defined and an attempt should be made to more closely approximate patterns of naturally occurring illness. To obtain this information we plan to use varying doses of organism for inoculation of the upper (nasal drops) and the lower (small particle aerosol) respiratory tract in order to determine the minimal dose that will produce infection and an illness response similar to natural disease. Moreover, only tissue culture grown organisms will be used for this purpose. The desired pattern of illness response is intermediate between that reported for families and that reported for military personnel. In families about 80% exhibit illness, about two-thirds are lower respiratory, and 20 to 30% exhibit abnormal chest x-rays. In the military only about 20 to 30% exhibit illness and 3 to 10% have pneumonia.

In addition to defining a challenge system, detailed examination of the immune response (humoral and cellular) will be performed in order to better elucidate the desired vaccine response.

Selection of Subjects: Recruitment of volunteers will be performed according to methods described (see Program Description). Volunteers who are hospitalized at The Methodist Hospital will receive $5 per day for the duration of their hospitalization (a rate set by the Department of Corrections). The financial reward and the opportunity to be free from work, guards, and to [illegible]ant environment, free time and good food available is an inducement to volunteer. However, it is significantly negated by the fact that volunteers who participate in studies at The Methodist Hospital must remain in prison for one additional day for each two days in the hospital. Since the study will be approximately 4 weeks in duration, the volunteer will be required to stay an additional 2 weeks in prison beyond his specified release date. Volunteers who participate at the Ramsey Unit of the Texas Department of Corrections will receive $35 for the study. This is considered by the Texas Department of Corrections officials to be an acceptable and not excessive incentive.

Discomfort to Subjects: Discomfort associated with obtaining specimens for isolation tests and blood and secretions for antibody assay and lymphocyte studies is minimal. Other discomforts will be those which will be associated with any illness that occurs. Illness may be of varying severity and include myringitis, afebrile and febrile pharyngitis, tracheobronchitis and pneumonia. Headache, malaise, and myalgias are common symptoms. Cough is the most characteristic symptom of M. pneumoniae infection. Illnesses may last for 5 to 7 days but not longer since specific treatment is available and will be given. Analgesics and other symptomatic medications will also be administered as indicated. Naturally occurring pneumonia and that seen previously in volunteers was usually limited to a single segment of one lobe and required 7 to 10 days for clearing. If pneumonia occurs, chest discomfort and significant cough may occur but the overall illness is rarely severe enough to require bed rest. Based on prior experiences in volunteers and descriptions of naturally occurring disease it is unlikely that more severe illness will be seen.

Purpose of Project: To develop a reproducible challenge system for volunteers which can be used for evaluation of experimental vaccines and chemotherapeutic agents.

Description of Study: Volunteers will be obtained according to procedures described under Program Description and brought to Methodist Hospital. Antibody-free individuals (growth inhibiting initially, more sensitive methods later) will receive thorough history, physical, laboratory and x-ray examinations to insure good health. They will then have the study explained to them in detail and will be asked to sign the enclosed consent form. In the event that an insufficient number of antibody-free individuals are available for the Methodist Hospital studies, the study may be completed at the Ramsey Unit of the Texas Department of Corrections but no studies will be done at that site until after initial aerosol inoculations are performed at The Methodist Hospital. The planned number of men is as follows:

Dose	No. Men in Each Group	
	Nasal Drops	Aerosol
1000 cfu	3	3
100 cfu	3	3
10 cfu	3	3
1 cfu	3	3
0.1 cfu	3	3

Aerosol inoculations are performed with a special aerosol inoculating apparatus fabricated for us which provides good control on dose. Following inoculation volunteers will be placed in isolation and examined once or twice daily for illness. Specimens will be obtained according to the enclosed protocol (see Attachment 1) and illness will be quantitated and recorded on the enclosed form (see Attachment 2). Shedding of the organism, the immune response, and illness response will be compared according to dose and method of inoculation of the infecting agent.

Potential Hazards and Safeguards: The major possible hazard associated with this study is the occurrence of pneumonia and, as stated, it is mild. Cold agglutinins will probably develop, but the likelihood of a titer occurring which is severe enough to warrant concern about hemolysis is extremely remote and has never been seen in previous volunteer studies. Pneumonia may be of varying severity and the moment illness is considered of significant severity (clinical judgment) or pneumonia clearly has occurred, the individual will be given tetracycline or erythromycin therapy. This therapy has been shown to produce an afebrile state within 48 hours in naturally occurring cases and to hasten the resolution of x-ray and abnormal signs in a large number of individuals. We believe that with this therapy and the conditions under which the study will be conducted that there is little hazard to the volunteer of either prolonged discomfort or occurrence of injury. Volunteers within the Methodist Hospital will have physicians and extensive medical care available in the event of unexpected complications. Volunteers at Ramsey will have immediate access to physicians and in the event that medical care facilities are considered inadequate, arrangements have been made for transporting the volunteer to The Methodist Hospital for more definitive care.

Benefits: Benefit to an individual volunteer consists of experiencing an infection, which he has a high likelihood of acquiring naturally, under the supervision of a physician. In addition, he will be contributing toward acquisition of new information on an important cause of human disease that may aid in development of new approaches to prevention and treatment.

Method of Obtaining Informed Consent: A detailed description of the study to be performed will be given to volunteers verbally and they will be asked to sign the enclosed consent form. They will be given an opportunity to ask any questions they desire and it will be made clear that they may remove themselves from the study at any time.

Robert B. Couch

Robert B. Couch, M.D., Principal Investigator

Acting Chairman, Department of Microbiology

Methodist Hospital

ATOR Couch, R.B., et. al.

Day	CBC	Serology Blood Chemistries	Urinalysis	Stool O & P	Nose/Throat Bacteria	Stools for Enteric Pathogens	BKG	Chest X-Ray	Sinus X-Ray		Throat Swab	Sputum		Anal Swab			Tube Clotted Blood For Antibody	Nasal Secretions	
Pre	X	X	X	X	X	X	X	X	X	X		X	X		X			2	X	X
0	X											X	X		X					
1																				
2	X											X								
3																				
4	X												X							
5												X								
6												X	X							
7	X																	1	X	X
8												X	X							
9																				
10	X											X	X							
11																				
12	X											X	X							
13																				
14	X					X						X	X					1	X	X
15																				
16	X											X	X							
17																				

BAYLOR COLLEGE OF MEDICINE
TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

DEPT OF MICROBIOLOGY
(713) 529-0951

VOLUNTEER'S CONSENT FORM

I understand that I am consenting to accept nasal drops or to breathe a mist which contains an infectious agent which I may or may not "catch." If I "catch it," it may or may not make me ill. If I develop an illness it may include earache, nasal obstruction and discharge, sore throat, hoarseness, cough, and chest pain. I understand that fever may occur and I may develop headache, weakness, muscle aches and loss of appetite. I have been told that pneumonia may also develop but that it is usually mild. Fever may last 2 to 4 days and symptoms for 7 to 10 days. I understand that other symptoms might occur and that it is possible, but unlikely, that illness will last longer than 10 days.

I understand that frequent nasal washings, throat swab and cough specimens, and blood drawings will be performed and used for tests. X-rays and other tests will be performed as indicated.

I understand that the information obtained from my participation in this study will be used for developing new methods for control of the infection. Furthermore, I understand that I will receive $5 per day for the duration of my time in the hospital. (Alternative for the Ramsey Unit: I understand that I will receive $35 for my participation at the completion of the study.

The proposed study has been clearly explained to me and I understand and accept the hazards involved. I have been given an opportunity to ask any questions I might desire and I understand that I have the right to withdraw from the study at any time I may choose.

Signature_____

Date_____

Witness_____

I have carefully explained the nature, demands, and foreseeable risks of the above study to the normal volunteer.

Signature_____

Date_____

RESPIRATORY DISEASE STUDY - III

ily Report of Illness

re all findings negative? XA@ →

Finding		Sev (1-3)
Photophobia	l	AB@ →
	r	AC@ →
Conjunct. erythema	l	AD@ →
	r	AE@ →
Bulbar erythema	l	AF@ →
	r	AG@ →
Pain	l	AH@ →
	r	AJ@ →
Tearing	l	AK@ →
	r	AL@ →
Other DT@		→
Ache	l	AM@ →
	r	AN@ →
Hemorrhage	l	AP@ →
	r	AQ@ →
Blebs, bullae	l	AR@ →
	r	AS@ →
Inflammation	l	AT@ →
	r	AU@ →
Other AV@		→
Sneeze		AW@ →
Obstruction		AX@ →
Discharge		AY@ →
Other AZ@		→

Site		Finding	Sev (1-3)
NOSE cont'd	PHYS EXAM	Obstruction l	BA@ →
		r	BB@ →
		Discharge	BC@ →
		Abnormal mucosa	BD@ →
		Other BE@	→
THROAT		Pharynx: redness	BF@ →
		exudate	BG@ →
		Tonsils: enlarged	BH@ →
		exudate	BJ@ →
		Pain on swallowing	BK@ →
		Sore throat	BL@ →
		Other BM@	→
NECK		Swollen glands	BN@ →
		Tenderness	BP@ →
		Other BQ@	→
TRACH		Pain & tenderness	BR@ →
		Other BS@	→
LARNX		Hoarseness	BT@ →
		Other BU@	→
CHEST		Pain	BV@ →
		Cough	BW@ →
		Sputum	BX@ →
		Splinting	DQ@ —
		Rales (moist)	DR@ —
		Rales (dry)	DS@ →

e 'D'
(9)

Date Y Y M M D D
(10) — — — — — —

tary time ___ ___ ___ ___
(16)

(over)

Hospital Stamp

...y Report of Illness continued

Finding	Severity (1-3)
Other BY@ →	
Anorexia	BZ@ →
Nausea	CA@ →
Vomiting	CB@ →
Pain or tenderness	CC@ →
Diarrhea	CD@ →
alpable liver	CE@ →
alpable spleen	CF@ →
Other CG@ →	
Rash	CH@ →
Other CJ@ →	
Feverish	CK@ →
Chills	CL@ →
Sweats	CM@ →
Muscle Aches	CN@ →
Malaise	CP@ →
Prostration	CQ@ →
Headache	CR@ →
(ier CS@ →	

	Finding	Severity (1-3)
SUMMARY	Patient's opinion: Does patient feel he is well? (Y or N) XB@ →	
	Examiner's opinion:	
	Rhinitis	CU@ →
	Pharyngitis	CV@ →
	Tracheobronchitis	CW@ →
	Pneumonia	CX@ →
	Systemic	CY@ →
	Cervical adenitis	CZ@ →
	Other DA@ →	

TEMPERATURE	Time	Oral	Rectal
	0-0400	DB@ →	DH@ →
	0400-0800	DC@ →	DJ@ →
	0800-1200	DD@ →	DK@ →
	1200-1600	DE@ →	DL@ →
	1600-2000	DF@ →	DM@ →
	2000-2400	DG@ →	DN@ →
	Additional readings: DP@ →		

Comments PP@ →

Signature of physician YA@ →

0	X											X	X		X					
1																				
2	X											X	X							
3																				
4	X											X	X							
5												X								
6												X	X							
7	X																	1	X	X
8												X	X							
9																				
10	X											X	X							
11																				
12	X											X	X							
13																				
14	X					X						X	X					1	X	
15																				
16	X											X	X							
17																				
18	X		X	X					X	X		X	X							
19																				
20												X	X							
21	X																	2	X	X
24												X	X							
26																		1	X	
35																		1	X	

ADDITIONAL INFORMATION FOR NIH

Title of Research Project: Development of a Reproducible and Effective Challenge System for Mycoplasma pneumoniae

Duration of Study: 6 months

Subjects: 30 adult (age 21-45) male prisoner volunteers
See Program Description for other qualifications and exclusions.

Additional Narrative Information:

2 b. Challenge agent: Mycoplasma pneumoniae.

Source: 1. Strain 10433: throat swab collected from a naturally occurring uncomplicated case of M. pneumoniae pneumonia in the Seattle Group Health Cooperative.

2. Strain 1428: throat swab collected from a Marine [illegible] Parris Island, North Carolina, with naturally occurring M. pneumoniae [illegible].

Preparation: 1. Strain 10433: harvest from third passage in human embryonic kidney tissue cultures maintained in MEM with 5% chicken [illegible].

2. Strain 1428: initially passaged twice in Hayflick-Clasrock PPLO broth and used for volunteer inoculations without complications. Present inoculum is harvest from two additional passages in human embryonic kidney tissue cultures maintained in MEM with 5% chicken serum and penicillin.

Purity: Purity of both pools was insured by the accompanying safety test procedure and by specific identification with Research Reference antiserum to M. pneumoniae. The latter identification was by growth inhibition with a

serum impregnated disc on agar and growth inhibition as measured by titration following an incubation period.

Titer: 1. Strain 10433 HEK_3: 7.5 log_{10}/ml
2. Strain 1428 BR_2 HEK_2: 8.0 log_{10}/ml

Challenge diluent: MEM with 2% human serum albumin

2 c. Blood: antecubital vein. Total volume within a 3 month period not to exceed 500 ml.

Nasal secretions: nasal rinse with 10 ml Lactated Ringer's Solution

Nasal wash: nasal rinse with 10 ml veal infusion broth

Throat swab, anal swab: standard procedures

2 d. Included in protocol.

BAYLOR COLLEGE OF MEDICINE
TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

TMENT OF MICROBIOLOGY AND IMMUNOLOGY
(713) 52[illegible]

VOLUNTEER'S CONSENT FORM

I understand that I am consenting to accept spray and nasal drops which contain an infectious agent, Mycoplasma pneumoniae, which I may or may not "catch." If I "catch it," it may or may not make me ill. If I develop illness it may include earache, nasal obstruction and discharge, sore throat, hoarseness, cough, and chest pain. I understand that fever may occur and I may develop headache, weakness, muscle aches and loss of appetite. I have been told that pneumonia may also develop but that it is usually mild. Fever may last 2 to 4 days and symptoms for 7 to 10 days. I understand that other symptoms might occur and that it is possible, but unlikely, that illness will last longer than 10 days. At the completion of the study, I will be given an antibiotic to aid in ridding me of the organism.

I understand that frequent nasal washings, throat swab and cough specimens, and blood drawings will be performed and used for tests. X-rays and other tests will be performed as indicated.

I understand that the information obtained from my participation in this study will be used for developing new methods for control of the infection. Furthermore, I understand that I will receive $50 for my participation at the completion of the study.

The proposed study has been clearly explained to me and I understand the hazards involved. I have been given an opportunity to ask any questions I might desire and I understand that I have the right to withdraw from the study at any time I may choose without prejudice to me.

Signature _____

Date _____

Witness _____

I have carefully explained the nature, demands, and foreseeable risks of the above study to the normal volunteer.

Signature _____

Date _____

Title: Development of a reproducible and effective challenge system for M. pneumoniae

Principal Investigator: R. B. Couch

1. A crucial component in this project is the certain definition of the participants as antibody-positive or antibody-negative. For this reason the Committee felt that the investigators should employ the most sensitive assay available for M. pneumonia antibodies.

2. Other safeguards included assay of the antigen preparations grown in HEK for Australian antigen and examination of the vaccine for reverse transcriptase. The committee was advised by the IDB staff that this latter assay could be done at Flow Labs.

3. The challenge assays should start with the lowest dose of Mycoplasma and proceed in an incremental manner.

4. Consent forms should name the organism and the disease under study. At the end of paragraph 1, the consent form should also state that persistant infections will be treated with appropriate antibiotic therapy.

5. Recommendations - Approval with the above modifications.

BAYLOR COLLEGE OF MEDICINE
TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

LEADING DEPARTMENT OF SURGERY
(713) 529-1551

November 8, 1972

Stephen B. Greenberg, M.D.
Department of Medicine
Baylor College of Medicine
Houston, Texas 77025

Dear Dr. Greenberg :

The Baylor Committee on Research Involving Human Beings is pleased to inform you that your research proposal Effect of Viral and Mycoplasmal Tract Infection on Pulmonary Function (GCRC)

on November 7, 1972 according to institutional guidelines with the following provisions:

1. Continued review will be required
   - ( ) a. After each subject's exposure
   - ( ) b. Quarterly
   - (.) c. Semi-annually
   - (x) d. Annually
   - (x) e. Change in Protocol
   - (x) f. Development of unexpected problems or unusual complications
   - (.) g. Other

2. Method of Review
   - (x) a. Questionnaire (example enclosed)
   - ( ) b. New Protocol
   - ( ) c. Interview with principal investigator
   - ( ) d. Other

Sincerely yours,

E. Stanley Crawford, M.D.,
Chairman, Committee on Research
Involving Human Beings

ESC:ib

Benefits:

The information gained from sequential study is unlikely to be of direct benefit to this volunteer. However, since the majority of volunteers are smokers the information gained from his initial study may indicate the need to cease smoking for his future health. Otherwise, information gained will relate to the influence of the common respiratory infections on pulmonary function acutely and will elucidate the severity and rate of recovery. The nature of any defect will indicate the need for symptomatic therapy during the common respiratory infections as well as the possible need for prophylactic measures.

Method of Obtaining Informed Consent:

A detailed description of the study to be performed will be given to volunteers verbally and they will be asked to sign the enclosed consent form. This explanation will include all known hazards associated with live agent challenge and the pulmonary function studies. He will be given an opportunity to ask any questions he desires, and it will be made clear that he can remove himself from the study at any time.

Stephen B. Greenberg, M.D.
Stephen B. Greenberg, M. D., Principal Investigator

Robert B. Couch, M. D., Investigator

Paul M. Stevens, M. D., Investigator

R. P. Williams, Ph. D., Acting Chairman
Department of Microbiology

Henry D. McIntosh, M. D., Chairman
Department of Medicine

pneumonia and to all others with this infection who are judged to be experiencing illnesses of moderate severity. Analgesics and other symptomatic medications will be administered as indicated.

Discomfort associated with pulmonary function studies include those associated with drawing of blood gases and swallowing of the esophageal balloon for compliance measurements. Spirometry measurements cause minimal discomfort. The volunteer will be asked to cooperate for about two hours each time these studies are obtained.

Potential Hazards to Subjects and Safeguards for Same:

In the event that pneumonia or any other severe illness is noted from M. pneumoniae inoculation, antibiotics will be immediately administered. The above described illness responses for influenza constitute those seen by us among approximately 300 artificially induced infections; specifically, pneumonia has never occurred. There seems little likelihood of a more severe illness occurring among these men than that described. Nevertheless, prior to inoculation, volunteers are told that pneumonia sometimes occurs with this virus infection. Inoculation will be by nasal drops (as opposed to aerosol) which we believe significantly reduces the hazard of pneumonia. Rhinovirus and Coxsackie A-21 (a common cold virus) infections have been produced in approximately 1,000 volunteers and there seems little reason to expect an untoward reaction.

Physicians will see all volunteers daily and twice daily if indicated. They will be on call 24 hours a day during the period of isolation and will administer therapy when indicated.

Arterial blood gases have been associated with local hematoma and damage to the peripheral artery in rare instances. A trained technician who performs this service in the hospital every day will obtain the blood gases. There is minimal discomfort from passing of the esophageal balloon. Vagal responses have been reported with this procedure. All pulmonary function studies including the passing of the esophageal balloon will be done by a physician trained in pulmonary diseases, and he will be in attendance during the entire procedure.

physician will be in attendance while all pulmonary function studies are being performed.

Selection of Subjects:

Recruitment of volunteers will be performed according to methods described (see earlier submitted Program Description). Volunteers who are hospitalized at The Methodist Hospital will receive $5 per day for the duration of their hospitalization (a rate set by the Department of Corrections). This financial reward and the opportunity to be free from work, guards, and to have pleasant environment, free time and good food available is an inducement to volunteer. However, it is significantly negated by the fact that volunteers who participate in studies at The Methodist Hospital must remain in prison for one additional day for each two days in the hospital. Since the study will be approximately 4 weeks in duration, the volunteer will be required to stay an additional 2 weeks in prison beyond the specified release date. This is considered by the Texas Department of Corrections officials to be an acceptable and not excessive incentive.

Discomfort to Subjects:

Discomfort associated with obtaining specimens for isolation tests and blood and secretions for antibody assay is minimal. Other discomforts will be those which will be associated with illness that occurs. Illness from rhinovirus or Coxsackie A21 infection will be a common cold, sometimes with fever. Illness from M. pneumoniae may be of varying severity and include myringitis, afebrile and febrile pharyngitis, tracheobronchitis and pneumonia. Headache, malaise, myalgias are common associated symptoms and cough is the most characteristic symptom of M. pneumoniae infection. Illness may last for 5 to 7 days but rarely longer. The range of illnesses to influenza include no illness, mild to severe afebrile upper respiratory illness with cough, and febrile upper respiratory illness with cough. Fever is of varying degree and may last from 1 to 5 days; respiratory symptoms occasionally last longer. During the febrile period, individuals may experience significant headache, myalgias, malaise, and anorexia. Specific treatment is available for M. pneumoniae and will be given to all individuals who develop

pathogenetic factor in the development of small airway obstruction. Certain viral and mycoplasmal infections may be more important than others in causing pulmonary dysfunction acutely and possibly permanently. The fact that we can now identify patients with early airway obstruction should allow us to determine the precise role of respiratory viral and mycoplasmal infections in the pathogenesis of airway obstruction.

Purpose of Project:

To determine if measurable alterations in pulmonary function occur during acute viral and mycoplasmal respiratory infections in normal volunteers.

Uniqueness of the Project and Probability of Publishable Results:

Minimal information is presently in the published literature on this subject. The opportunity to study volunteers in a sequential fashion and for defined infections should provide precise frequency and severity data that will unquestionably be publishable.

Description:

Volunteers will be obtained according to procedures described under the previously submitted Program Description for Normal Volunteers and brought to The Methodist Hospital. Antibody-free individuals will receive a thorough history, physical, laboratory and x-ray examinations to insure good health. Approximately 6 normal adult volunteers will be given a rhinovirus (see renewal approval, June 20, 1972), or Mycoplasma pneumoniae, (see CRC protocol approval, 9/13/72). Later studies may include Influenza and Coxsackie A21 (previously approved agents). Blood and nasal secretions will be obtained before inoculation and at 2 and 4 weeks following vaccination. Volunteers will be examined daily and twice daily if indicated, by a physician. Volunteers will remain in isolation for a variable period depending upon the agent under study.

Routine pulmonary function studies plus static and frequency dependent compliance, closing volume and arterial blood gases will be obtained in these volunteers. The pulmonary function tests will be performed before inoculation, during acute illness and at approximately weekly intervals thereafter as needed. A

Title: Effect of Viral and Mycoplasmal Respiratory Tract Infection on Pulmonary Function

Principal Investigator and Associates: Stephen B. Greenberg, M. D., Robert B. Couch, M. D., Paul Stevens, M. D., and John Pettigrove, M. D.

Departments Involved: Microbiology and Medicine

Other Research Support: None

Duration of Study: Indefinite

Number of Subjects: Approximately 6 per agent with an estimated total of 25

Duration of Occupation of GCRC Bed: 3-1/2 weeks

Maximum number of patients to be hospitalized: 6

Background Information:

Recent studies have shown that acute exacerbations of chronic airway disease may be due to upper respiratory viral infection. During upper respiratory viral infections infections, pulmonary function deteriorates further in many of these patients. However, the role of upper respiratory viral infections in the pathogenesis of chronic airway disease has not been clearly defined.

Recent developments in measuring pulmonary function and specifically in measuring changes in resistance of small airways has provided the necessary tools for understanding the natural history of chronic airway obstruction. Frequency dependence of compliance and closing volumes are two new measurements that are sensitive enough to demonstrate early reversible obstruction of small airways.

Recent evidence indicates that some acute viral infections of the upper respiratory tract cause peripheral airway obstruction four to eight weeks after clinical recovery. The abnormalities were reversed after an additional six weeks. It has also been observed that clearance of inhaled small particles was markedly prolonged during acute viral infection of the upper respiratory tract. Both of these observations lend support to the view that repeated infections may be an important etiologic and

BAYLOR COLLEGE OF MEDICINE
TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

DEPARTMENT OF MICROBIOLOGY
(713) 529-0551

VOLUNTEER'S CONSENT FORM

I understand that I am consenting to accept nasal drops or to breathe a mist which contains an infectious agent which I may or may not "catch." If I "catch it," it may or may not make me ill. If I develop an illness it may include earache, nasal obstruction and discharge, sore throat, hoarseness, cough, and chest pain. I understand that fever may occur and I may develop headache, weakness, muscle aches and loss of appetite. I have been told that pneumonia may develop but that it is usually mild. Fever may last 2 to 4 days and symptoms from 7 to 10 days. I understand that other symptoms may occur and that it is possible, but unlikely, that illness will last longer than ten days.

I understand that frequent nasal washings, throat swab and cough specimens, and blood drawings will be performed and used for tests. X-rays and other tests will be performed as indicated.

I understand that I will have several lung function tests during my hospital stay. These lung tests will require my breathing into a tube many times and swallowing a thin rubber tube.

I understand that the information gained from this study will be of no direct benefit to me except that a thorough evaluation of my lung function may indicate some needed treatment. The information gained may be of benefit to other people. I understand that I will receive $5 per day for the duration of my time in the hospital.

The proposed study has been clearly explained to me and I understand and accept the hazards involved. I have been given an opportunity to ask any questions I might desire and I understand that I have the right to withdraw from the study at any time I may choose.

Signature_____

Date_____

Witness_____

I have carefully explained the nature, demands, and foreseeable risks of the above study to the normal volunteer.

Signature_____

Date_____

Addendum to protocol entitled "Effect of Viral and Mycoplasmal Respiratory Tract Infection on Pulmonary Function"

1. Change in Principal Investigator - to Robert B. Couch, M. D.

2. This protocol is paired with the protocol entitled "Effect of Natural Viral and Mycoplasmal Respiratory Infections on Pulmonary Function and Immunologic Function of the Lower Respiratory Tract." The immunologic studies in that protocol involve measurement of T and B lymphocyte function, thymidine by stimulated lymphocytes, new methods for assessing antibody, and polymorphonuclear leukocyte function. Although these assays are approved for other protocols, we wish to add them to the present protocol since the studies are paired with study of naturally occurring disease.

All studies are performed on peripheral blood and nasal secretions so the consent form does not change. Performance of the studies will not alter the limitation on blood to be obtained (no more than 500 cc during the study).

Robert B. Couch, M. D.
Principal Investigator

Vernon Knight, M. D.
Chairman, Department of
Microbiology and Immunology

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TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

DEPARTMENT OF INTERNAL MEDICINE
(713) 520-4951

January 8, 1975

Robert B. Couch, M.D.
Department of Microbiology & Immunology
Baylor College of Medicine
Houston, Texas 77025

Dear Dr. Couch :

The Baylor Committee on Research Involving Human Beings is pleased to inform you that your research proposal ADDENDUM: Effect of Viral and Mycoplasmal Respiratory Tract Infection on Pulmonary Function (GCRC)

was approved on January 7, 1975 according to institutional guidelines and provided it receives the unaltered approval of the institutional committee in which it is involved.

1. Continued review will be required
   - ( ) a. After each subject's exposure
   - ( ) b. Quarterly
   - ( ) c. Semi-annually
   - (x) d. Annually
   - (x) e. Change in Protocol
   - (x) f. Development of unexpected problems or unusual complications
   - ( ) g. Other

2. Method of Review
   - (x) a. Questionnaire (example enclosed)
   - ( ) b. New Protocol
   - ( ) c. Interview with principal investigator
   - ( ) d. Other

Sincerely yours,

Harold Brown, M.D.,
Chairman, Committee on Research
Involving Human Beings

HB:ib

Title of Research Proposal: Lymphocyte Cytotoxicity to Influenzavirus in Peripheral Blood of Normal Volunteers

Principal Investigator and Associates: Stephen B. Greenberg, M. D.
Robert B. Couch, M. D.

Department Involved: Microbiology and Immunology

Location of Research: Baylor College of Medicine
Ramsey Unit of the Texas Department of Corrections

Other Research Support: NIH/NIAID Contract No. 73-2506

Duration of Study: 6 months to 1 year

Number of Subjects: 20 - 30

Duration of Occupancy of GCRC Bed by Each Subject: None

Maximum Number of Patients to be Hospitalized at One Time: None

Background Information:

The role of lymphocytes in host response to influenza is uncertain apart from their participation in antibody formation. A rather limited body of evidence currently suggests that cell-mediated responses may contribute to host resistance in viral infections of the respiratory tract. Lymphocytes from the lung or from other lymphoid tissue are capable of producing mediators of cellular immunity in response to viral antigens. Although there is no good evidence that cell-mediated immunity is a critical determinant in influenza or other respiratory tract infections, specific and non-specific activation of lymphocytes during infection must be looked for as necessary components of host resistance.

Lymphoid cells have effector functions in certain tissue-damaging immune reactions. A number of *in vitro* models have been designed in order to throw light on the mechanism of these tissue-damaging reactions. Lymphoid cells from

sensitized donors will destroy tissue culture cells carrying the antigen and this has been used to develop an in vitro test of lymphocyte mediated cytotoxicity.

Chromium-51 labelled, influenzavirus infected tissue culture cells can be examined for specific lysis when inoculated with peripheral lymphocytes from antibody positive and negative individuals. If specific lysis does occur in individuals with previous proven influenza infections, this would suggest that lymphocyte cytotoxicity plays a part in host resistance to this virus.

Purpose of Project:

To determine if lymphocyte mediated cytotoxicity occurs in influenza antibody negative and positive individuals.

Uniqueness of the Project and Probability of Publishable Results:

There is presently no available information concerning lymphocyte mediated cytotoxicity in individuals with previous influenzavirus infection. The information obtained in this study will be suitable for publication.

Description of Study:

Volunteers will be asked to give approximately 100 ml (one-fifth pint) of blood obtained by venipuncture. Hematocrits will be performed and no person with a hematocrit less than 40 will be asked to volunteer. The same individual will not be asked to contribute this 100 ml of blood more often than once every 2 weeks, and the total shall not exceed 500 ml for any 3 month period. The 100 ml of blood will be collected in heparinized plastic tubes. The lymphocyte population will be separated using a ficoll-hypaque gradient. The lymphocytes will be counted and a specified number will be added to tubes containing ^{51}Cr labelled, influenzavirus infected, tissue culture cells. At various incubation times, the amount of ^{51}Cr released from the virus infected cells will be measured.

Selection of Subjects:

Medical Center personnel will be asked to volunteer through a posted notice. Prisoners from the Ramsey Units, Texas Department of Corrections, will be asked to volunteer by posted notice, also. Volunteers will received $5.00 for obtaining this blood sample.

Discomfort to Subjects:

The only discomfort from the procedure is that associated with venipuncture.

Potential Hazards to Subjects and Safeguards for Same:

Venipuncture can be associated with extravasation of blood into surrounding tissue. Trained personnel will draw the blood and check for proper local hemostasis. No one with a history of a bleeding disorder will be asked to volunteer.

Method of Obtaining Informed Consent:

A description of the study to be performed will be given to the volunteers verbally by the principal investigator and they will be asked to sign a consent form (see enclosed form). The volunteer will be given the opportunity to ask any questions that he desires, and it will be made clear that he can remove himself from the study at any time.

Stephen B. Greenberg, M.D.

Stephen B. Greenberg, M. D.
Principal Investigator

Vernon Knight

Vernon Knight, M. D.
Chairman, Department of Microbiology
and Immunology

BAYLOR COLLEGE OF MEDICINE
TEXAS MEDICAL CENTER
HOUSTON, TEXAS 77025

[illegible] OF MICROBIOLOGY AND IMMUNOLOGY
[illegible]

VOLUNTEER'S CONSENT FORM

I understand that I am consenting to have 100 ml (5 tablespoons) of blood drawn from a vein in my arm.

I understand that occasionally blood may leak into surrounding tissue after such a procedure and cause some discomfort.

I understand that the information obtained from my participation in this study will be of no direct benefit to me but may help us to understand how we are protected from the "flu." Furthermore, I understand that I will receive $5 for the donation of my blood.

The proposed study has been clearly explained to me and I understand and accept the hazards involved. I have been given an opportunity to ask any questions I might desire and I understand that I have the right to withdraw from the study at any time I may choose.

Signature _____

Date _____

Witness _____

I have carefully explained the nature, demands, and foreseeable risks of the above study to the normal volunteer.

Signature _____

Date _____

Title of Research Proposal:	Immunoresponsiveness during Influenza Virus Infection
Principal Investigator:	Thomas R. Cate, M. D.
Collaborating Investigators:	Robert B. Couch, M. D. J. A. Kasel, Ph. D. Roger D. Rossen, M. D. Howard R. Six, Ph. D. Vernon Knight, M. D.
Department:	Microbiology & Immunology
Granting Agency:	NIH contract AI-42528
Period of Grant:	June 26, 1974 - June 25, 1979
Location of Study:	Ramsey Units of the Texas Department of Corrections, and Baylor College of Medicine

Background:

Several reports have suggested that infection with certain non-oncogenic viruses can cause immunosuppression as manifested by decreased delayed hypersensitivity responses, decreased *in vitro* proliferative responses of lymphocytes to both phytohemagglutinin and heterologous antigens, and impairment of both primary and secondary antibody responses to heterologous antigens (1).