

## CHAPTER 4

### PHYSICAL EXAMINATION METHODOLOGY

The 1992 followup examination was provided to 2,233 invited and scheduled participants, who traveled to the examination site in La Jolla, California. The examination consisted of the following major elements:

- Review-of-systems questionnaire
- Psychological testing
- Physical examination
- Laboratory testing
- Specialized testing (e.g., phlebotomy for measurement of serum dioxin)
- Psychological and medical outbriefings.

The Combat Experience Questionnaire and skin, hair, and eye color determinations (components of the 1985 followup examination) were conducted for all participants who did not attend the 1985 or 1987 followup.

The Air Force carefully prescribed the details of the above examination elements. Clinical variations were neither desired nor authorized; all proposed examination procedural changes were reviewed in detail by Air Force technical and contractual personnel prior to the start of the examinations. An important objective of the entire physical examination process was to ensure that bias was not created by any procedural change, and this objective was carried out successfully. The requirement to maintain blind examinations was particularly stringent. The clinical staff was prohibited from knowing or seeking information as to the group identity (i.e., Ranch Hand, Comparison) of any participant. At the end of the examination, each participant was asked to note on the critique form whether such information was sought by any member of the clinical or paramedical staff. Three participants indicated that an examining physician had asked them about specific duties in Southeast Asia (SEA); two of these participants later stated that they had not been questioned but rather had volunteered information in casual conversation. The third participant could not be identified because he chose to remain anonymous.

### EXAMINATION CONTENT

Examination content, as designed by the Air Force, emphasized detection of medical endpoints suspected of being associated with exposure to phenoxy herbicides, chlorophenols, or dioxin. In 1985, the Air Force used findings of the Baseline examination to direct refinement of the 1985 followup examination. Since the 1987 followup examination was initiated prior to the full analysis of the data from the 1985 examination, most modifications to the examination format and procedures were founded upon quality control (QC) issues and the desire to make the clinical content of the examination more responsive to the medical needs of the participants.

Based on the results of the 1987 followup examinations, the 1992 examination content was expanded to include additional testing for glucose-intolerant participants. Other additions to the examination content used updated medical testing equipment and procedures such as vibrotactile threshold, Doppler pulses, and testicular ultrasound. The general content of the 1992 physical examination and psychological test battery is shown in Table 4-1. The complete laboratory test series is displayed in Table 4-2.

As in the Baseline and the 1985 and 1987 studies, QC requirements for both laboratory testing and clinical procedures were extensive. Although details are provided in Chapter 6, the following categories summarize the extent of the emphasis on quality. For laboratory testing, single reagent lots and control standards were used when practical, duplicate specimens were routinely and blindly retested, testing overlaps were mandatory when test reagent lots were changed, and fast initial response cumulative sum (FIR CUSUM) were used to rapidly detect any subtle drift in test results over time. The Scripps Clinic and Research Foundation (SCRF) clinical team was carefully instructed to assure clinical quality. Quality control included the following elements:

- The examination process was pretested.
- Detailed clinical inspection techniques were employed by SCRF, Science Applications International Corporation (SAIC), and Air Force physicians and personnel.
- Preprinted mark-sense examination forms were used.
- Clinical quality assurance (QA) meetings were conducted to detect and correct problems.
- The examiners were unaware of the exposure status of the participants.

Based on the 1985 followup, clinical QC enhancements were made to improve measurement techniques in the 1987 followup and continued in the 1992 followup. The digit preference noted in systolic and diastolic blood pressure readings in the 1985 followup led to the use of automated blood pressure recording; all other parameters of the blood pressure readings (e.g., sitting position, three recordings, nondominant arm at heart level) were not changed. The 1987 skin-test-reading QC plan was continued. That plan included the following elements:

- Refresher training for readers.
- A reading of the four skin tests of all participants by both readers, each blind to the results of the other.
- Ten percent of all tests were reread by each of the readers, each blind to the previous reading.

**Table 4-1.  
Elements of the 1992 Followup Physical Examination**

<b>Elements</b>	<b>Remarks</b>
General Physical Examination	Internist
Neurological Examination	Neurologist
Dermatologic Examination	Dermatologist
Electrocardiogram	Resting, 4-Hour Fasting and Nicotine Abstinence
Chest X-Ray, KUB, Testicular Ultrasound	Radiologist
Immunologic Studies	40% Random Sample
Skin Test Studies	80% Sample
Psychological Evaluation:	
Millon Clinical Multiaxial Inventory (MCMI)	
Symptom Checklist 90-Revised (SCL-90-R)	
Jenkins	
Pulmonary Function	Internist with Subspecialty in Pulmonary Disease
Audiometry Examination	Audiologist
Vision Screening and Tonometry	Technician
Patient Outbriefing and Discussion of Individual Results	Internist, Medical Diagnostician, and Ph.D. Psychologist
Vibrotactile Threshold	Technician
Doppler	Technician

**Table 4-2.  
Laboratory Test Procedures of the 1992 Followup Physical Examination**

<b>Day 1 Tests: Monday and Wednesday</b>	
Sedimentation Rate	Alkaline Phosphatase
Prothrombin Time	Direct Bilirubin
Protein Profile	Total Bilirubin
Complete Blood Count (includes RBC indices)	High Resolution Electrophoresis
Creatinine	LDH
Creatine Phosphokinase	Glycated Hemoglobin
Urinalysis (including urobilinogen)	Hepatitis Panel*
Cholesterol	High-Density Lipoprotein Cholesterol
T-Cell Clones**	Triglycerides
Immunofixation***	Serum Amylase
Rapid Plasma Reagin	Stool Hemocult
Lupus Panel (includes anti-thyroid antibodies)	Prostate-Specific Antigen
Flow Cytometry**	2-Hour Urinary Postprandial Glucose
Rheumatoid Factor	Glucagon
AST	Insulin
ALT	2-Hour Postprandial Glucose
GGT	Proinsulin****
Fasting Glucose	C-Peptide****
	Islet Cell Antibodies****
<b>Day 2 Tests: Tuesday and Thursday</b>	
Serum ACTH	Total Testosterone
Free Testosterone	Estradiol
Follicle Stimulating Hormone	Serum Luteinizing Hormone
Thyroid Stimulating Hormone	T <sub>4</sub>
Sex Hormone Binding Globulin	Blood Draw for Dioxin*****

- \* Testing to be performed by Air Force.
- \*\* Participants scheduled for special immunology testing.
- \*\*\* An immunochemical method for identifying monoclonal proteins in serum.
- \*\*\*\* Testing to be performed only on known or newly diagnosed diabetics. Individuals with a 2-hour post-prandial glucose > 140 mg/dl are considered newly diagnosed.
- \*\*\*\*\* Participants scheduled for dioxin testing by CDC.

- A weekly report citing numbers and proportions of participants with possible anergy, reversal of induration-erythema measurements, and untoward skin reactions or other reading problems (e.g., participant refusal).

In addition, skin test forms developed for the 1987 followup were used to facilitate accurate recording and transcription. Specific clinical criteria were formulated to require consultation with an allergist, and the skin test measurement criterion for possible anergy, consistent with current World Health Organization (WHO) guidelines, was adopted for the clinical interpretation of all skin test readings.

To encourage participation in future followup studies, participant rapport-building techniques were added in 1985; these included participant critique forms and recreational opportunities afforded to any accompanying family members. These were continued for the 1992 followup, and additional aspects, such as unscheduled time for the participant and a number of preventive medicine evaluations were added including tonometry, vision screening, audiometry, and occult blood testing.

In the 1992 followup, the preventive medicine examinations were expanded to include human immunosuppressant virus (HIV) testing, prostate-specific antigen (PSA) testing, and kidney, urethra, and bladder (KUB) x rays. Proctosigmoidoscopy, as well as treadmill tests, were made available to participants for a nominal fee, and accompanying family members were offered the opportunity to use the clinic facilities at a discounted rate.

## CONDUCT OF EXAMINATIONS

All examinations, from May 1992 to March 1993, were conducted in accordance with the Examiner's Handbook, provided in Appendix C. Excluding weeks with national holidays, two groups of participants, averaging approximately 28 per group, were examined weekly.

A demanding logistics effort was required to contact, transport, and examine 2,233 study participants. Pre-examination contact consisted of making telephone calls to recruit participants, determine special requirements (e.g., wheelchair assistance, weekend examination schedule), and arrange transportation. Once scheduling was reasonably firm, the SAIC logistics coordinator sent each participant a detailed information package outlining dietary requirements, a stool occult blood testing kit (Hemoccult®), inbriefing schedules, important telephone numbers, a request for medical records, and local maps designating examination-site dining and recreational facilities.

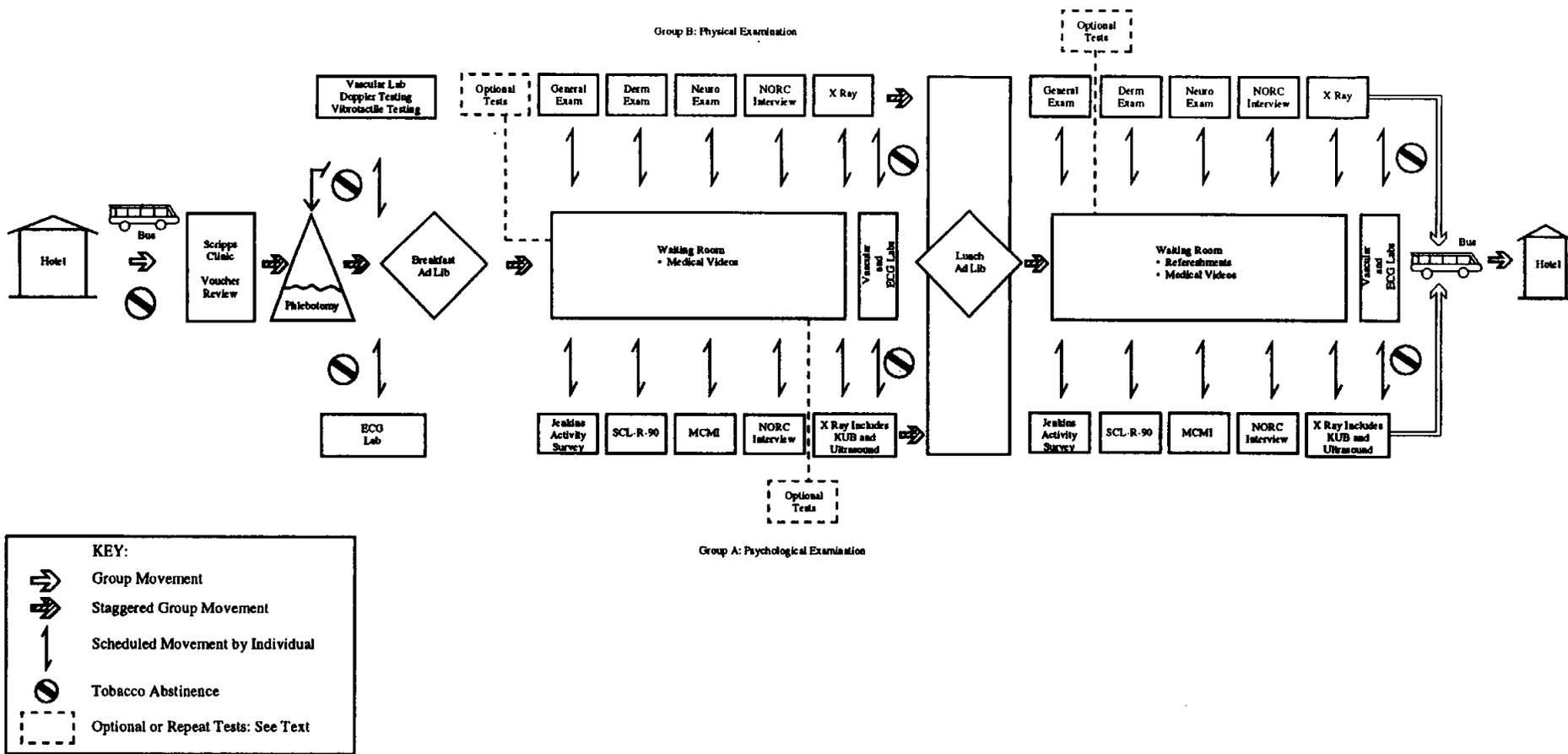
Figures 4-1 and 4-2 outline participant flow for the first and second examination days. As depicted in these figures, each morning of the first 2 days, the current group of participants was transported to the SCRF clinic, having fasted and abstained from tobacco and caffeine since midnight the previous evening. In addition, alcohol was strictly prohibited from 72 hours before the first day of the examination through the second day of the examination. On the first day, each participant was given an individualized 3-day schedule outlining his medical, interviewing, and laboratory appointments. The schedule carefully noted the specific required periods of fasting and tobacco abstinence (see Figures 4-1 and



Day Two

AM

PM



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Figure 4-2. Flow Diagram of Day Two Followup Interviews and Physical Examination

4-2) for generalized periods in relation to electrocardiograph (ECG) testing. Although the clinic schedules were generally assigned at random, consideration was given to smokers and diabetics because of the fasting and abstinence restrictions.

As in the 1987 examination, schedules were printed with specific directions to aid participants in locating clinic departments, although for many tests, participants were escorted from the waiting room. Throughout the examination day, time was provided for waiting-room activities (i.e., renewal of past friendships, discussions of experiences in SEA, consumption of refreshments when permitted, and completion of paperwork). On the third day of the examination, skin tests were read, and the participants received outbriefings from a psychologist and medical diagnostician. Upon completion of these debriefings, the participants were paid their stipend, reimbursed for travel expenses, and transported to the airport.

As noted previously, the SCRF clinical team was specifically chosen for this project. In total, 15 board-certified physicians in internal medicine, neurology, and dermatology participated in the general, specialty, and diagnostic examinations. In addition to the 15, there were 13 radiologists, 5 allergists, 2 pulmonologists, and 2 cardiologists who performed tests and interpreted results. To reduce observer variability, turnover in the clinical and paramedical staffs was minimized during the 10 months of examinations. One SCRF physician served as the Project Medical Director, responsible for the scheduling, conduct, and QC of the examinations. All examining physicians were introduced to the mark-sense examination forms prior to the pretest examination. To minimize recording errors, the layout of the form was designed to parallel the flow of the clinical examination. Because data transcription was not permitted, each physician was responsible for filling in the bubbled form. To a large extent, the use of these mark-sense forms and subsequent QC measures were the primary reason for a clean clinical data set. A complete set of forms is provided in Appendix C.

As in the 1987 followup, special testing included delayed hypersensitivity skin tests and immunologic tests. Skin tests for four antigens were administered in a standardized manner: *Candida* (1:1,000 weight/volume, 0.1 ml intradermal), mumps (2 complement-fixing units), Trichophyton (1:1,000 weight/volume, 0.1 ml intradermal), and staph-phage lysate ( $6-9 \times 10^6$  colony-forming units of *S. aureus* and  $0.5-5 \times 10^7$  staphylococcus bacteriophage plaque-forming units). Allergy-immunology nurse specialists measured the indurations by the standard pen method\* at 48 hours after injections. For unusual cases of anergy or severe local reactions, physician consultation was provided. Detailed immunologic testing (see Table 4-2) was conducted on approximately 40 percent of the participants. These participants were identified by the last digit of their participant study identification number used for previous testing, thus establishing a longitudinal connection between examinations. Workload factors mandated blood draws on the second day for one-half of the selected

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\*Starting 1 to 2 cm away from the margin of the skin test reaction, a medium ball point pen is used to trace a line toward the center of the skin test reaction. When the line reaches the margin of area, resistance is incurred, and the line is stopped. A similar line is drawn from the opposite direction of the first line. The distance between the two lines is measured.

group. Because of the high proportion of adverse reactions at the first blood draw during the Baseline examination and the potential of these reactions to adversely effect the aviator status of many of the participants, reclining blood-bank chairs were used for all phlebotomy procedures. The chairs were introduced initially in the 1985 study and kept blood-draw incidents to a minimum. The individuals chosen for in-depth immunological testing were excluded from skin testing to avoid interference with the immunologic results. The immunologic tests were subjected to highly structured QC procedures set forth by the Air Force.

New testing introduced in the 1992 followup included: estradiol, rheumatoid factor, serum amylase, lupus panel, serum adrenocorticotrophic hormone (ACTH), and glycated hemoglobin. In addition, known and newly diagnosed glucose-intolerant participants received C-peptide, proinsulin, and islet cell antibody tests.

## CHAPTER 4 REFERENCES

1. Patterson, D.G. Jr., L.L. Needham, J.L. Pirkle, D.W. Roberts, J. Bagby, W.A. Garrett, J.S. Andrews, Jr., H. Falk, J.T. Bernert, E.J. Sampson, and V.N. Houk. 1988. Correlation between serum and adipose levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 50 persons from Missouri. *Archives of Environmental Contamination and Toxicology* 17:139-43.