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PROSPECTIVE MEDICINE OPPORTUNITIES IN AEROSPACE MEDICINE.(U)
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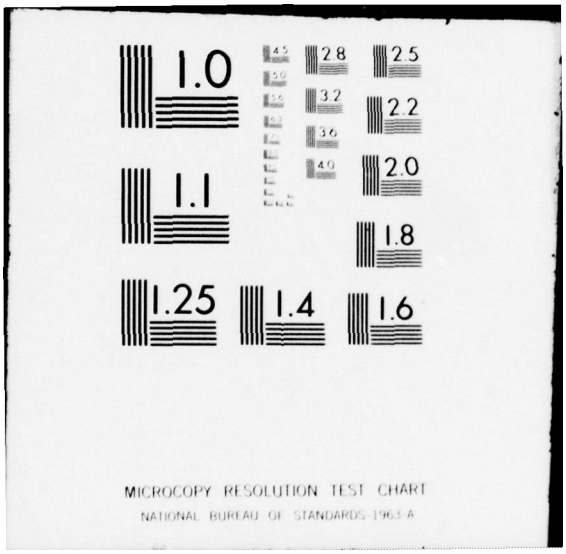
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PROSPECTIVE MEDICINE OPPORTUNITIES IN AEROSPACE MEDICINE

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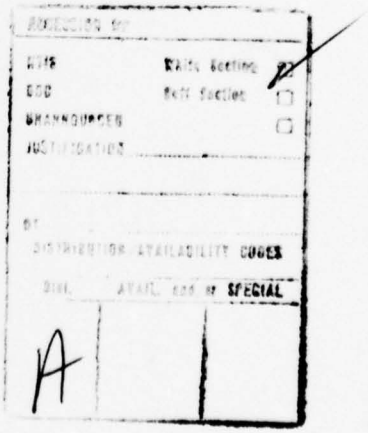

PREFACE

The purpose of prospective medicine is to identify the propensity for disease development at a stage long before clinical pathology can be detected and then to intervene in the process to positively modify prognosis. Proper utilization of currently available data related to readily identifiable risk factors would allow concentration of medical interest within a relatively small segment of the population from which the majority of medical problems will become manifest, without sacrifice of good medical care for the remainder, and without detriment to flying safety.

Prospective medicine promotes intervention in the disease process before the disease becomes clinically significant and thus offers a real opportunity to significantly reduce manpower losses. The prospective medicine approach could also form the basis for significant revision of current selection and retention criteria for the military aircrewmen.

The following papers discuss various applications of prospective medicine techniques to the practice of aerospace medicine. These papers dealt with studies conducted in the special population of military aircrew on the prevalence/incidence of findings, including multiple risk assessments, correlation of these with disease risks, and the results of efforts to modify the risk for disease and its clinical manifestations.

John H.TRIEBWASSER, Col., USAF, MC, FS
Session Organizer

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THE CANADIAN FORCES
LIFE QUALITY IMPROVEMENT PROGRAMME

by

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Summary

The Canadian Forces has introduced a Life Quality Improvement Programme (LQIP) to counteract the ravages of diseases which arise from risks prevalent in most lifestyles in Western society. These so called "diseases of choice" will be discussed in terms of their antecedent "self-imposed risks". A discussion of the programme concept is given centering around 15 factors and six philosopies deemed essential for success. The programme will evolve in three phases: planning, trial and general implementation, under the direction of the Planning Cell. Central in the programme is the individual assessment which will be composed of various biomeasurements, a Health Hazard Appraisal, a health questionnaire and an interview. In support of this central assessment will be an educational/promotional campaign and a variety of supportive clinics. A general discussion of how we see the programme operating will conclude this paper. We feel that the programme will be cost effective, but that the most important benefits will be in terms of enhanced individual health and overall operational fitness of the Canadian Forces.

Introduction

Over the past few years there has been a dramatic shift in the emphasis of health care, from one of medical intervention when health is lost, to one of prevention before disease becomes manifest. Although partly due to the precipitously rising cost of the health care system, the principal factor was the realization that the big killer diseases in our society are, to a large degree, "diseases of choice" - that is, diseases resulting from those "self-imposed risks", prevalent in most Western lifestyles. Table I gives an outline of such self-imposed risks with some of the so-called "diseases of choice" resulting therefrom.

TABLE I

SELF-IMPOSED RISKS AND RESULTANT DISEASES OF CHOICE

The following is a list of the more common self-imposed risks prevalent in most modern lifestyles, and some of the diseases of choice resulting from each. These diseases are at least partly preventable through lifestyle change.

1. Faulty Nutrition

   a. Over-eating - leading to obesity and its consequences, such as diabetes, high blood pressure, coronary artery disease, back problems.

   b. Inappropriate Diet - especially of highly refined carbohydrates, saturated fats and food additives - leading to hardening of the arteries, high blood pressure, diabetes, cancer, dental caries, obesity and its consequences; and

   c. Inadequate Diet - through malnutrition and fad diets - leading to assorted deficiencies and low physical resistance and performance.

2. Lack of Exercise - leading to poor physical condition, and contributing to obesity and its consequences, notably heart disease.

3. Lack of Recreation, Relaxation, Sleep and Relief from Domestic and Socio-economic Pressures - contributing to those diseases of stress, i.e. poor mental health, suicide, high blood pressure, heart disease, peptic ulcers, and other psychosomatic conditions.

4. Smoking - contributing to bronchitis, emphysema, heart disease, various cancers including lung, larynx, mouth, throat, and bladder.

5. Misuse of Alcohol - leading to alcoholism and its socio-economic consequences, accidents, obesity, malnutrition, cirrhosis of the liver, brain degeneration, various cancers including throat and liver.

6. Environmental Pollution - leading to noise damage, depression, poisoning and contributing to poor hygiene and its consequences.

7. Misuse of Other Drugs (both licit and illicit) - leading to addiction/ dependence and other socio-economic consequences, accidents, malnutrition, overdosing, and mental diseases.

8. Faulty Hygiene - leading to veneral diseases, skin disorders and infestations, food poisoning.

9. Deficient Safety - Consciousness - leading to accidents, drownings, poisonings - both in the work environment and otherwise.

The reasoning behind such a shift is simple: if one can prevent the diseases of choice, not only will the overall health of society be enhanced, but countless sums of money will be saved from one of the largest of government budgets.

Accordingly, this preventive trend in health has reached into many quarters, and numerous efforts to do something positive have evolved. Nationally, the most noteworthy of such efforts was the publication by Health and Welfare Canada in 1974 of "A New Perspective on the Health of Canadians", the introduction of Health Hazard Appraisal (HHA), and the "Fit Kit", and the subsequent launching of "Operation Lifestyle". Presently, hardly a day goes by without either an article on the subject in the popular or medical press, or the introduction of a new campaign or programme.

Because the health of service personnel is so key to the operational fitness and readiness of any armed force, this preventive approach to health is particularly relevant. Indeed, certain commanders in the Canadian Forces have been openly disturbed by the prevalence of certain risk factors, such as obesity and substandard fitness as manifest by the failure rate in, or medical excusal from, our 1½ mile annual fitness evaluation. And when the Defence and Civil Institute of Environmental Medicine (DCIEM) did a random survey in 1970 and found that not only was the average serviceman no more physically fit than the average citizen, but also significantly overweight, the truth was bared. To counteract such a state of affairs in the Canadian Forces, several independently-conceived programmes were set up and data gathered from these established a high prevalance of "self-imposed risks" in the Canadian Forces. To estimate the overall extent of health problems caused by such self-imposed risks, the Director of Preventive Medicine looked at assessable costs in terms of mortality, releases, absenteeism, hospitalization and sick leave in a typical year - 1973 - (Table II).

TABLE II

ESTIMATED COST OF DISEASES OF CHOICE

For replacement of the dead	$ 5,900,000
For replacement of the released	5,800,000
For hospitalization	9,700,000
For wages, etc, of the hospitalized	2,700,000
For wages, etc, of those on sick leave	1,500,000
TOTAL	$25,600,000

When such costs are totalled, it can be seen that in excess of $25 million was spent for these potentially preventable causes. The figures are conservative because they do not include such things as time off taken but not recorded, loss of experience, decreased morale and productivity, etc. Such a situation demanded action.

The Programme Concept

Although encouraged by the success of various civilian programmes, and by individual efforts within the Canadian Forces, it was obvious that such local efforts would be even more effective if they were part of a comprehensive, centrally co-ordinated and standardized programme. The LQIP was designed to be such a programme. Because it is intended to be a comprehensive effort to alter human behaviour, a task extremely difficult to execute, several factors are deemed essential to its success:

a. Voluntary Participation. Based on the premise that health is an individual responsibility and changes in lifestyle are thus the individual's choice.

b. Available to All Service Personnel and Their Dependents. Based on the fact that one person is a functioning member of a family unit, and changing one, demands changes in the others.

c. Multi-disciplinary Approach. Based on the idea that health is everyone's business and that the task at hand is too big to be handled by any one group which probably does not have all the expertise necessary; also, based on the premise that a co-operative effort among all principals will be synergistic

d. Central Co-ordination. To enable the sharing of ideas and experiences and allow one central group of experts to remain up-to-date on happenings around the world.

e. Example and Support from Top Down. If leaders show the way and support the programme, changes of success are enhanced.

f. Support to, and Co-ordination of, Existing Programmes. To gain from the experiences of such programmes and promote co-operation.

g. Basic Standardization. To enable a continuum of participation when one moves from base to base.

h. Practicability. Must solve problems rather than create them.

j. Feasibility. Must be able to adapt to the variety of units within the Canadian Forces.

k. Adequate Data Collection. To enable the determination of the effectiveness of the programme and to monitor progress of it.

m. Adequate Promotion and Education. To avoid misconceptions and unreal expectations.

n. Adequate Resources Available. Based on the fact that you cannot expect someone to do something unless he has the wherewithall to do it.

p. Appropriate Follow-up. Based on the established need for this to maintain motivation, as well as to monitor both individual and programme progress.

q. Utilization of the Most Up-to-Date Behavioural Modification Techniques. Including use of tools such as HHA, and adoption of the concept that we are catalysts not therapists in this endeavour.

r. Implementation in Phases. To ensure adequate planning and trial before large commitments are made.

The Evolution of the Programme

LQIP will evolve in three phases: Phase I - planning; Phase II - trial; and Phase III - implementation.

a. Phase I. This is the planning phase wherein the National Defence Headquarter's (NDHQ) Planning Cell (see later) is putting together a model of the LQIP and forecasting the personnel and equipment necessary to implement the programme. It is estimated that this will be finished by January, 1978.

b. Phase II. This phase will be a trial study at two representative Canadian Forces bases. The NDHQ Planning Cell will co-ordinate this phase working closely with base and command personnel. This phase will give valuable data on the effectiveness of the programme, together with feedback which will allow modification to the programme in terms of approach, personnel and facilities required. At the end of this phase, which is estimated to commence in January, 1978, and run for about one year, the data will be analyzed and a report sent for approval of the programme. With approval, Phase III will commence.

c. Phase III. This phase will be the implementation of the programme throughout the Canadian Forces. The Planning Cell will co-ordinate such implementation and be available for consultation to the bases and stations as the need arises. At this time, the LQIP will integrate the numerous smaller, independently conceived programmes already in existence.

Implementing Personnel

We in the military are indeed fortunate since we have a variety of professionally trained resource people that can be used in a programme of this nature. Thus, we are able to carry out the multi-disciplinary approach to this field that we deem so essential to our programme's success. The following is a list of those people that we see as being directly concerned with LQIP:

a. Planning Cell. Composed of four specialist officers at NDHQ in the fields of medicine, nutrition, physical education and sociology, and under the co-ordination of the medical member, this cell will be responsible for the initial planning, implementation, evaluation and continuation of the LQIP. It will be responsible to the Surgeon General of the Canadian Forces through the Director of Preventive Medicine. The Planning Cell will have available to them consultants in a variety of specialties as required.

b. Research and Development Cell. This Cell will consist of the Exercise Physiology Section at DCIEM and will provide the Planning Cell with a research and development capability as the need arises. This Cell will be primarily responsible for the assessment and evaluation of various techniques used in the LQIP, and the collection, storage and analysis of data.

c. Command Level Cell. It is anticipated that the existing command staff will be able to monitor and exert command responsibilities on a regional basis without any increase in establishment. This will be achieved by ensuring maximal co-ordination of effort by command staffs.

d. Base Implementation Cell. This Cell will consist of the base medical officers, base dental officers, public health nurse, preventive medicine technicians, personnel selection officer, food services officer, physical education officer and instructors, padres, drug education officer, social work officer, general safety officer, flight safety officer and others interested. This Cell will be responsible to the base commander for the assessment, appraisal and follow-up of those individuals entered into the LQIP on their base. It will set up resource clinics and programmes as necessary, and will collect the LQIP data. The intoduction of periodic medical screening techniques to replace routine physical examinations will release personnel for the LQIP. As most of these personnel are on base strength already, there may not be a need for staff augmentation depending on the size of the base population.

Figure I is a flow diagram which illustrates how the programme will function basically. Initially, an intensive educational and promotional campaign will take place using a variety of media. This campaign will both introduce LQIP and furnish information on self-imposed risks, diseases of choice and how LQIP can assist in healthful change. It is anticipated that by the time each unit is capable of commencing an active programme, this initial campaign will recruit participants. The rest of the participants will probably become involved through referral from several sources, including work, fitness assessments, counselling and medical and dental visits; however, we hope that a significant portion will come from the "ripple effect", that is, a friend telling a friend telling a friend, etc.

Central to the programme is a means of assessing the health status of participants. Such an assessment not only supplies the individual with a means of judging his present lifestyle and subsequent healthful change, but will supply data to evaluate the overall effectiveness of the programme. This assessment will have four interdependent segments:

a. Biomeasurement. Risk-related parameters such as height, weight, blood pressure, pulse, skin folds, grip strength, aerobic fitness (using a bicycle ergometer), lung function and laboratory tests (e.g. serum cholesterol and triglycerides).

b. Health Hazard Appraisal (HHA). A computerized health assessment based on mortality data which gives the participant an indication of the risks to health that his lifestyle presents, and what can be done to reduce such risks.

c. Questionnaire. An individual health questionnaire concerning such matters as nutritional habits, life stresses, and other risk factors not covered in HHA.

d. Interview. Designed to amplify the questionnaire segment, answer any queries the participant may have, and individualize and personalize the initial assessment and subsequent programme.

Such an initial assessment will furnish a frank and detailed personal appraisal, including the presence of self-imposed risk factors which could adversely affect future health, and will form the basis of the individual programme the participant can follow to enhance his health.

An integral part of the individual's programme will be the resource clinics available to assist him in changing those habits in his lifestyle that he chooses to change after his initial assessment. These clinics, with appropriate specialists involved, will be based on the proven "group" principle. A partial list of some of the more important of these clinics is as follows:

a. Physical Fitness Clinic - assistance with a personally or family tailored fitness programme;

b. Nutrition Clinic - providing counsel on food purchasing and dietary requirements;

c. Alcohol/addiction Clinic - furnishing treatment and rehabilitation for drug and alcohol problems;

d. Smoking Clinic - aiding in the cessation of smoking;

e. Obesity Clinic - assisting in weight control; and

f. Mental Health Clinic - assisting in such things as stress, relaxation and recreation.

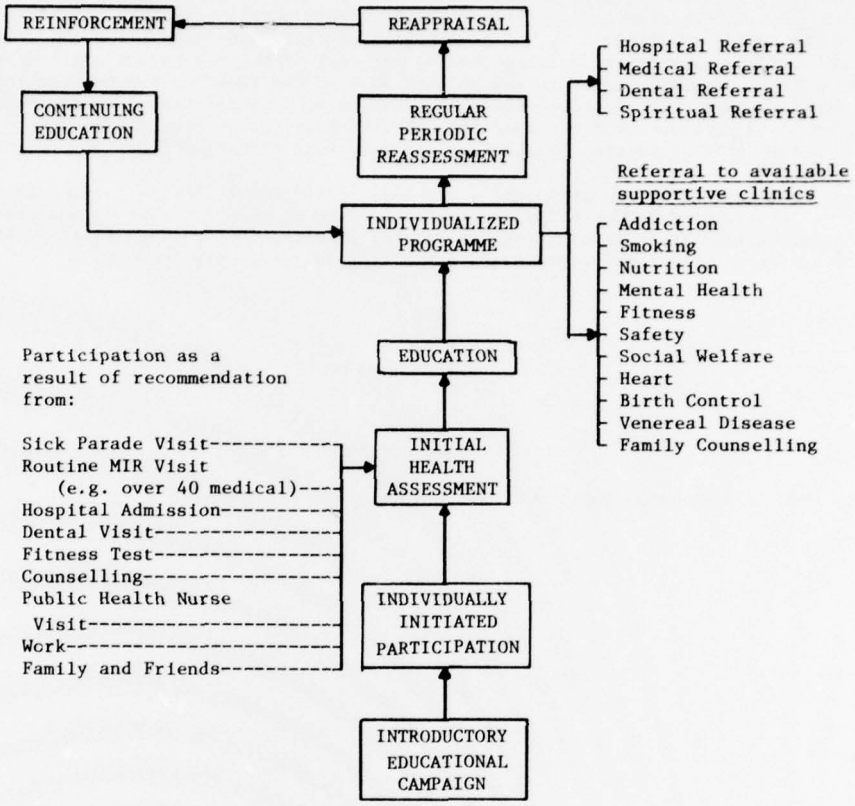
Such clinics will have educational and supportive elements and will use modern principles of behaviour modification.

Regular, periodic re-assessment will follow, with concomitant continuing education and encouragement for the purpose of maintaining the motivation necessary for continuation in the programme. Assistance in this regard will come from the base cell and the clinics available. Each participant's programme will be continuously modified as need and circumstance dictate.

FIGURE I

LIFE QUALITY IMPROVEMENT PROGRAMME FLOW DIAGRAM

The chain of events comprising the LQIP illustrating how the programme commences initially, and how it is maintained. The list of clinical facilities available is tentative and, therefore, subject to deletions/additions as experience will dictate. It should be pointed out that several of the clinics are already in existence and will be incorporated into the programme.



Key Philosophies

A final note on the execution of a programme such as LQIP is in order. Because we are dealing with the alteration of human behaviour we feel that several concepts are key to the programme's success. They are:

a. Negativism! Too much stress has been placed on how many lifestyles can adversely affect health. In this area, we are bombarded constantly with warnings. And this technique is not very successful if the anti-smoking campaign is any indication. The positive aspects of change seem much more fruitful ground to cultivate since it gives people something to which to look forward.

b. Fanaticism! We must remember that just because one person is committed to a particular way of life, does not mean that that way is necessarily the best for others. Fanaticism in our efforts is not only unnecessary, but usually ends up in an effect opposite to the one desired.

c. Impatience! Another unwanted trait! We must remember what we are trying to change are long-established habits that are usually deeply engrained in the lifestyle of the individual. We should not expect changes in such areas to come about overnight. We would do well to remember the old chinese proverb: "The man who removes a mountain begins by carrying away small stones."

d. Rights! We must constantly remind ourselves that each person has a right to the lifestyle of his choice, regardless of the harm it may cause him. Our obligation is to educate the individual as to the health significance of his lifestyle, offer him an alternative and the facilities for change, and then allow him to make up his own mind on the value of such change. In changing behaviour the individual himself must be convinced of the value of such change, and be committed to it, before the change becomes permanent.

e. Example! Good example cannot be underestimated when it comes to altering habits in others. The old principle in man management of never asking anyone to do something that you would not do yourself holds true here. Of course, if we are to set good examples, we must first be convinced of the value of the programme, and then commit ourselves to it.

f. People! Finally, it must be remembered constantly that we are dealing with people - not cases, or numbers, or examples, or machines - but people - human beings who have their own problems, their own families, and their own lives. It only makes common sense that when we try to do something for people, we must be human ourselves.

Potential Impact

As stated earlier in this presentation, a conservative estimate of some $25 million of public funds is expended annually as a result of diseases of choice in the Canadian Forces. Programmes similar to, but less encompassing than, that described in this paper have been undertaken independently at two military bases in Canada, without the need for additional staff. These purely voluntary programmes attracted about 30 per cent of the base populations. It has been predicted that, had these bases had available to them the wherewithall outlined in this paper, greater than 50 per cent of the population would have entered the programme voluntarily. It would be naive to expect that half of the Canadian Forces population would adopt such a programme initially, let alone successfully. But, even if one-fifth undertake this programme successfully, about $5 million could be saved from the Canadian Forces budget each year. The costs of the required increases in establishments, facilities, and equipment should not come near to that sum.

However, notwithstanding the programme's probable cost benefit, the most significant results will be evident in terms of increased productivity, reduction in loss of man hours due to absenteeism, premature retirement and death, and the obvious advantages and far-reaching implications to the individual, to say nothing of the enhanced operational fitness and capability of our Forces.

DISCUSSION

The discussion that followed this paper was unfortunately not recorded.

THE ROLE OF PHYSICAL EXAMINATIONS AND EDUCATION IN PROSPECTIVE MEDICINE

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Summary

NASA's prospective medicine program, which has existed for over a decade, has two principal elements: physical examinations and an educational program for health awareness. Participation in the voluntary physical examination program is increasing. In 1976, 13,621 employees were given partial or complete examinations in NASA Health Units. This was over one-half of the total NASA work force. From the 941 examinations performed at NASA Headquarters in 1976, 522 new principal findings were detected. New equipment and techniques in exercise EKG, tonometry, and colonoscopy were partially responsible for this high rate. The health awareness program includes consultations with physicians, new training devices and courses, health bulletins, and special screening programs. Epidemiological studies, now underway, will be used to evaluate the health awareness programs.

Introduction

The goals of prospective medicine are to promote health and to control in advance those forces which threaten the health of an individual and, thus, decrease work efficiency and performance. The National Aeronautics and Space Administration (NASA) has had a prospective medicine program for over a decade. The NASA program has two principal elements. The first of these is the physical examination. An annual physical is offered to all employees in order to monitor the overall health status of the work force and to identify diseases at an early stage when they can be treated easily and effectively. The second element is an educational program for health awareness. Included within this program are periodic screening efforts for specific diseases such as hypertension.

The NASA prospective medicine program is growing. A review of its history shows that it has identified and controlled specific health problems. There is also a growing conviction that health awareness programs do produce individual health benefits and higher productivity. We are now turning to the techniques of epidemiology to provide concrete evidence of the efficacy of these efforts.

NASA Physical Examination Program

NASA Health Units offer physical examinations, on a voluntary basis, to all employees. For those with special risk factors, a complete physical examination is offered every year, or more often if necessary. For other employees, a partial examination, consisting of elaborate laboratory screening, is given annually, and a complete examination is provided at least every third year. The complete physical examination was described previously (Jones, 1977). Participation in this voluntary examination program is increasing. Figure 1 shows that participation is now almost 70% in males and over 50% in females. The age distribution of the population of NASA employees and the percentage of those examined within each age range are shown in Table 1.

NASA Headquarters personnel are a relatively healthy working population. The 1976 death rate was 3.2 per 1000 employees. This is less than half the rate of 6.9 expected when the comparison group is the whole U.S. population with the same age and sex distribution as our employees.

Table 2 shows the number of complete and partial physical examinations given by NASA Health Units, agency-wide, during 1976. The number of physicals given (13,261) shows that over one-half of the total NASA work force was examined during a one-year period. Table 2 also shows the differential manner in which some of the principal diagnostic procedures were used.

Headquarters employees account for 941 of the NASA physical examinations given in 1976. Table 3 presents the principal findings of these examinations for male and female employees. For those problems deemed correctable, the employee was referred to his private physician for therapy. Emergency care is, of course, offered at the NASA facility.

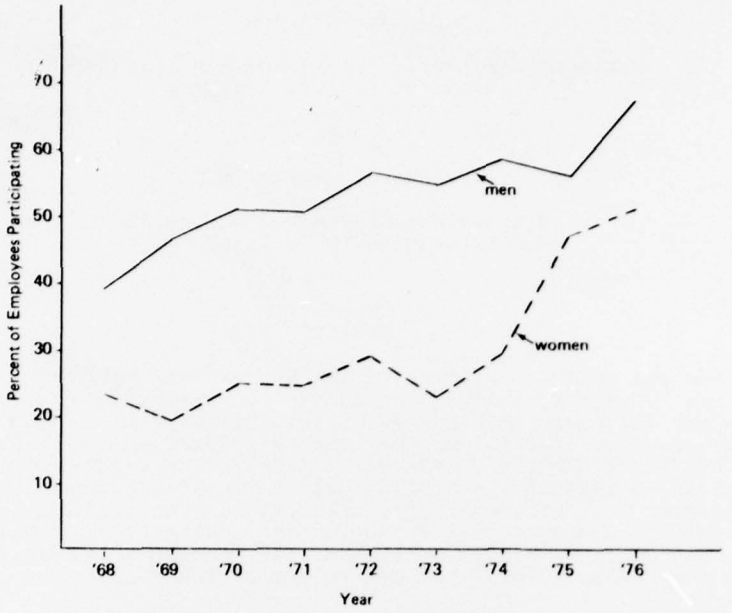

Figure 1: NASA Headquarters Physical Examination Program: Participation Rate by Sex and Year

Table 1

Age Distribution of Permanent Employees
(NASA Headquarters - 30 June 1976)

Age Range	Male	Female	Total	Percent Examined
Under 25	10	112	122	52.1
25 - 29	35	120	155	57.0
30 - 34	61	95	146	64.2
35 - 39	91	66	157	65.3
40 - 44	156	60	216	62.9
45 - 49	198	51	249	57.3
50 - 54	217	64	281	65.0
55 - 59	144	30	174	60.7
Over 60	54	18	72	67.2
Total employees	966	616	1572	
Average age	46.9	36.0	42.6	

Table 2

NASA Physical Examination Program
(CY 1976)

Examinations	Number
Complete	9,889
Partial	3,732
Total	13,621
Diagnostic Procedures	
Exercise EKG	5,555
Chest X-ray	13,879
Proctosigmoidoscopy	2,794
Audiometry	15,494
Breast Examination	1,837
Pap Stain	705

Table 3

Principal Diseases and Medical Findings in
644 Male and 297 Female Employees
(1976)

Condition	Male				Female			
	Total	%	New	%	Total	%	New	%
Neoplasms								
Benign	9	1.4	9	1.4	12	4.0	12	4.0
Malignant	4	.6	4	.6	3	1.0	3	1.0
Heart Disease	18	2.7	4	.6	3	1.0	1	.3
Respiratory Disorders	24	3.7	22	3.4	3	1.0	3	1.0
Hypertension	108	16.7	28	4.3	23	7.7	6	2.0
Uro-genital Disorders	69	10.7	69	10.7	71	23.9	65	21.9
Thyroid	11	1.7	11	1.7	15	5.0	11	3.7
Hernia								
Hiatal	10	1.6	10	1.6	3	1.0	3	1.0
Inguinal	11	1.7	8	1.2	0	0	0	0
Diabetes Mellitus	13	2.0	3	.5	6	2.0	5	1.7
Obesity	128	19.9	74	11.5	33	11.1	15	5.0
Anemia	13	2.0	13	2.0	42	14.1	42	14.1
Neuroses	10	1.6	9	1.4	3	1.0	3	1.0
Multiple Sclerosis	1	.2	1	.2	0	0	0	0
Hearing Loss	365	56.7	55	8.5	65	21.9	10	3.4
Gastro-Intestinal Disorders	16	2.5	8	1.2	15	5.0	15	5.0

As can be seen in Table 3, the examinations yielded many new findings, even when they were done on an annual basis. Of the 941 Headquarters employees examined, 328 new principal findings were obtained in male employees and 194 in females. Follow-ups were also made for 482 disorders which had been identified previously in males and 203 cases in females. This gave a total of 1,107 positive principal findings of new and old disorders in Headquarters personnel in 1976.

These data illustrate the value of annual examinations. Many of the disease processes discovered were time-critical. It is believed that the seven malignancies were found in time for successful intervention. Many of the 21 benign neoplasms needed differential diagnosis.

Improvement of Examination Equipment and Techniques

Prospective medicine applied in a modern industrial or Federal health facility can make an important contribution to employees' health. Equipment and techniques more advanced and elaborate than those usually found in private physician's offices can be employed. Equipment with new capabilities makes possible more reliable measurements and extends the examination field. A discussion of three examinations in which advanced equipment or techniques were used at NASA follows.

Exercise EKG

There are considerable efforts underway to demonstrate the value of exercise testing in identifying the early stages of heart disease. Froelicher and coworkers at the U.S. Air Force School of Aerospace Medicine (1975) have reported on studies involving their treadmill testing experience in the U.S. Air Force. They conducted an epidemiologic study of 1,640 asymptomatic men screened with maximal treadmill testing. It was found that 20% of those with abnormal treadmill responses developed coronary heart disease. This finding demonstrates that maximal treadmill testing is a valuable screening technique for coronary heart disease.

In another longitudinal study, Dr. Myrvin H. Ellestad (1977) of the University of California reported that the incidence of heart disease in individuals with a positive stress test in his laboratory over a six year period was 61%. Only 7% of those with a negative response developed heart disease.

One argument against the use of exercise EKG's involves cost. However, when cost factors are related directly to medical effectiveness, this argument loses its validity. In a study at the NASA Ames Research Center (LaDou, Sherwood, and Hughes, 1975), the cost per positive finding for exercise EKG was $56. This compares favorably to a cost of $115 for a positive finding identified by a resting EKG.

At NASA Headquarters, 6-hour dynamic EKG's are routinely administered before treadmill testing is done. It has been found that the dynamic tests are more effective than the treadmill tests in detecting abnormal coronary responses. Several arrhythmias and ischemia cases have been discovered using dynamic EKG's.

Tonometry

Early detection of glaucoma in clinical testing is quite important and saves the vision of many people each year. Unfortunately, the test for glaucoma is considered objectionable by many, since it usually involves direct application of the testing device to the cornea. In order to make the testing more acceptable to employees, NASA recently purchased a Non-Contact Tonometer (Model 12415, manufactured by the American Optical Corporation). This device reliably measures the intraocular pressure by applanation using an air pulse increasing linearly with time. Although subjects are surprised by the puff of air, they experience no pain and give favorable reports about the test. In 1976, NASA Headquarters employees were screened using this device. The pressures recorded varied from 3 mmHg to 34 mmHg, as can be seen in Table 4. Individuals with recorded pressures over 27 mmHg were referred to opthalmologists. Several glaucoma patients got weekly readings at the request of their opthalmologists. In addition to the screening program, follow-up examinations were conducted. These follow-ups were accomplished reliably and with a minimum of lost work time.

Colonoscopy

Another examination which is most cost effective in the yield of positive findings is colonoscopy. New equipment extends the field of view as much as 165 cm through the use of a flexible fiberoptic colonoscope. At NASA Headquarters, a 65 cm fiberoptic scope (Flexible Sigmoidoscope, Model F91-S, manufactured by the American Cystoscope Makers, Inc.) about 1 cm in diameter has been in use since November, 1976. In the first seven months of use, 62 employees were examined. Six cases with significant findings were detected. All but one of the lesions discovered were beyond the visibility with the usual 25 cm x 25 mm rigid sigmoidoscope. The age distribution and positive findings of those tested are listed in Table 5.

Two of the employees with positive findings have had surgery, and malignant pathology was established. The early discovery of these lesions improved the prognosis. Thus, the benefits from the use of this device amply justify its cost. In 1976, 132 protoscopies were also performed with the standard sigmoidoscope. Of these, the yield was only seven cases; all were benign.

Table 4

Distribution of Measures with
Non-Contact Tonometer on
NASA Headquarters Employees

Pressure (mmHg)	No. of Cases	
	Right Eye	Left Eye
3 - 4	0	1
5 - 6	1	0
7 - 8	4	4
9 - 10	36	38
11 - 12	100	124
13 - 14	184	196
15 - 16	201	188
17 - 18	163	144
19 - 20	82	79
21 - 22	39	38
23 - 24	21	16
25 - 26	8	4
27 - 28	2	3
29 - 30	2	2
31 - 32	0	1
33 - 34	0	1

Health Awareness

A principal goal of prospective medicine is the maintenance of good health through an ongoing educational program. The most effective means of education should be discussions with the physician after an examination. All NASA examinations, whether partial or complete, are followed by informative discussions. One innovation involving patient education by physicians is the female breast simulator for instruction in self-examination procedures. The simulator is a shell, containing four different nodules, that fits over the patient's chest.

Cardiovascular Pulmonary Resuscitation Training is also given by many of the NASA centers. The purpose of this instruction is to provide trained personnel at the scene of a mishap so resuscitation can begin before medical help arrives. The goal is to have a trained team on each floor in each building occupied by NASA employees.

Other methods of education which are being employed to improve the health of NASA employees are bulletins, posters, and brochures. Recently, NASA Headquarters began preparing bimonthly Health Bulletins, brochures which provide specialized information in easily-read form for employees. Examples, as can be seen in Figure 2, are "Fiber in Your Diet," "Hypertension and Dietary Sodium," and "Know Your Odds -- Have Your Blood Pressure Checked." Bulletins planned for the future will address relaxation, back pain and lifting, exercise, smoking, and nutritional principles.

Each bulletin provides a three or four paragraph description of the problem, a brief overview of available objective data concerning benefits to be gained from good health practices in this area, a straightforward indication of the specific steps to be taken by an employee if he wishes to follow these health guidelines, and references for further reading. Using the bulletin, the employee may weigh the evidence himself. This approach is preferable for scientific and engineering populations. Hence, reaction to the bulletins by NASA employees has been quite favorable. This approach is illustrated by the lead paragraphs from the "Hypertension and Dietary Sodium" bulletin:

EFFECTS OF SODIUM

"The average American diet is high in sodium content because of our heavy reliance on convenience foods and high consumption of snack foods which contain a lot of salt. The amount of sodium the human body requires is very small, perhaps only one-twentieth of the amount we normally consume. This excess sodium intake may be an important factor in the upward trend of national heart disease rates.

"There is a direct relationship between the amount of sodium in one's diet and the risk of developing hypertension (high blood pressure). The strongest

Table 5

Principal Findings of Colonoscopy

November 1976 - June 1977

Age	# Examined	Description - Principal Findings
34	1	
40	1	
42	2	One case of two benign polyps at 23 cm and 14 cm levels.
43	1	
44	1	
46	1	
48	1	
50	5	
51	4	
52	6	
53	3	
54	8	One case of diverticula at 60 cm. One case malignant pedunculated polyps, 2.5 cm in diameter at 30 cm; lobulated, with areas of redness.
55	5	One case of malignant polyps at 55 cm, 1.5 cm in diameter, pedunculated on a thick stalk.
56	3	
57	6	
58	5	One case of benign sessile polyp, 1.3 cm in diameter at 38 cm and a benign columnar pedunculated polyp, 4 cm in diameter, 1.5 cm high, with granular hemorrhagic surface.
59	4	One case of benign 2-3 mm sessile adenomatous polyp at 25 cm.
60	1	
61	3	
62	1	

evidence for the link between sodium intake and hypertension comes from comparisons of prevalence of hypertension in a number of the world's populations. Many of the world's "low blood pressure populations" are preindustrial peoples who consume only minute amounts of sodium. Those groups which have become more acculturated increase their use of salt and experience a corresponding increase in hypertension.

"There is further evidence on the sodium-high blood pressure relationship. The earliest effective treatment for hypertension was discovered in the 1940's by Kempner who treated hypertensive patients with a rice-fruit diet. The therapeutic effect of this diet was found to be due to its very low sodium content."

Another educational effort which has been very successful involves special screening programs. While screening is somewhat redundant to the physical examination program, it does reach up to 20% of the population which does not participate in the examination program. The screening programs at NASA are based on new scientific evidence and modern technology.

Within the past decade, significant advances have been made in understanding disease processes and the conditions and exposures which make people subject to these diseases. Results of large-scale longitudinal investigations, such as the U.S. National Institutes of Health Framingham study, are being used by the medical community to assign objective risk factors to individuals with certain traits and practices. This means, of course, that the relationship between measurable medical states, such as cholesterol levels, and personal practices, such as smoking habits, can be used to predict the likelihood of specific medical disabilities. This information can be used to establish meaningful health awareness programs to reduce these risk factors for employees.

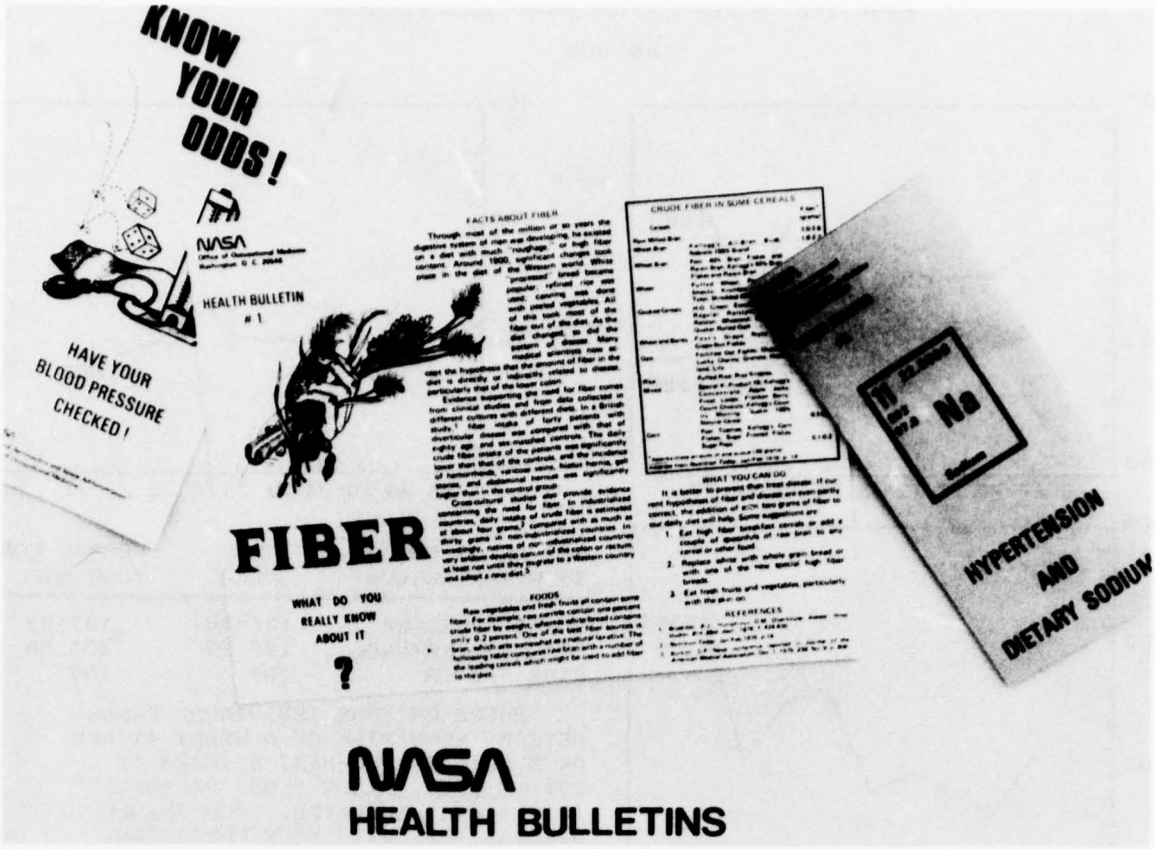

Figure 2: Examples of Health Bulletins

A special hypertension awareness program has been conducted for the past two years at NASA Headquarters. The program coincided with the National Hypertension Awareness Program of the National Institutes of Health. In both 1976 and 1977, the month of May was proclaimed Hypertension Awareness Month. During this month, NASA's goal was to obtain blood pressure measurements for as many Headquarters employees as possible (independently of physical examinations). Each person who was examined received a computer printout which showed his blood pressure readings and his trend over the years for which medical records were available in NASA, his cholestrol level and trend, and the risk of his having some cardiovascular difficulty in the next eight years. A sample computer printout is shown in Figure 3. Educational material was also distributed to each participant. The entire transaction involved only three minutes per person. The response of our employees was most encouraging. On opening day each year, there frequently were as many as 20 to 30 persons waiting in line for their turn to be examined.

In 1977, over 1,000 determinations were made on employees; some of these were repeats. Of those screened, 176 individuals (19%) had blood pressures elevated above the normal range. Depending on the pressure noted, these individuals received one of two messages on the printout. The first message indicated that the blood pressure was slightly elevated and advised a recheck. The second message was much stronger and advised individuals to seek medical attention for their problem. Follow-up procedures are underway.

Discussion

The NASA prospective medicine program has been in effect for over a decade and is continually being modified to achieve additional improvements in employee health. The two principal components of this program are periodic physical examinations and an ongoing educational program.

The annual screening program for employees focuses on problems which can be detected early and which generally respond to appropriate therapy. Dr. Morris F. Collen, a well-known specialist in preventive medicine, has noted that the purpose of physical examinations in an industrial setting should be to identify diseases which he calls "potentially postponable," such as heart trouble predicted by high blood pressure, rather than diseases against which medical science has devised treatment of only limited effectiveness (McQuade, 1977). The NASA program is based on this philosophy.

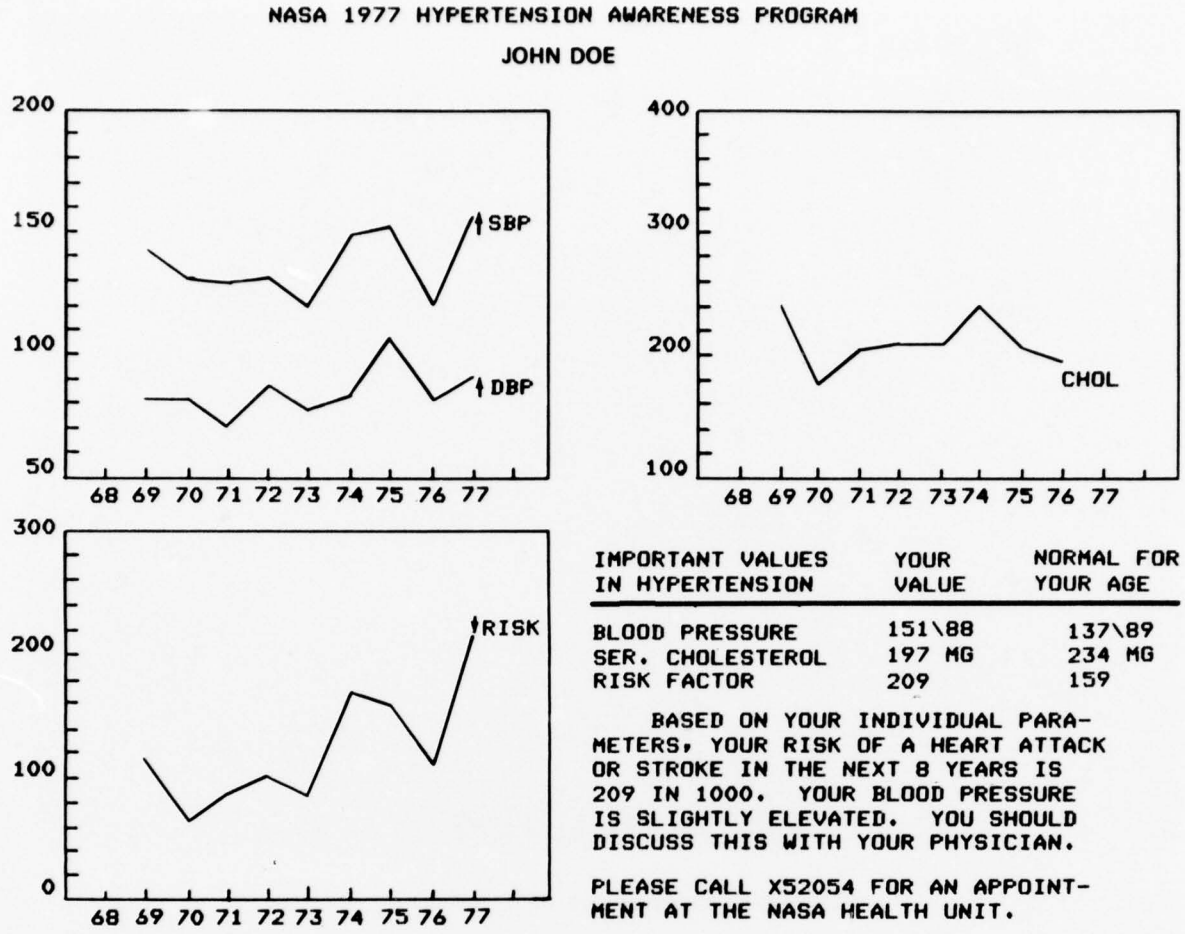

Figure 3. Computer Printout in Hypertension Screening Program (1977)

The role of an educational program, such as provided through the Health Bulletins, is more difficult to assess than are the direct results from physical examinations. In future years, however, we are optimistic that epidemiological procedures will clearly show that the development of an employee health awareness program is an integral and complementary part of a prospective medicine program predicated principally on physical examinations.

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DISCUSSION

Triebwasser: Do you perform sigmoidoscopy as a routine procedure irrespective of your employee's age?

Jones: No. We offer it to all. The General Accounting Office has investigated employee health programs throughout the government and criticized many of the agencies for selectively offering services to select groups and individuals. Two years ago NASA departed from this policy. As a result, a young secretary, only 18 years of age will have a sigmoidoscopy if she so desires. Very few accept; but we really try to sell it if they are in the right age group.

MacIntyre: In your preprint you mentioned exercise electrocardiograms. Do you routinely do this and if you do, what do you do with your positive results?

Jones: We give an annual examination to all employees and included in that is a standard resting electrocardiogram; and, at least every third year, we offer an exercise electrocardiogram using the treadmill. But at headquarters, we give a dynamic electrocardiogram, meaning a longitudinal one lasting at least six hours prior to the treadmill. On the treadmill, we only stress these people to 85% maximum because as you are well aware, there is quite a bit of controversy on just who or when some of these exercise ECG's should be done. On one end of the spectrum is a group that will only do these tests right next to a coronary care unit. On the other end there are other people that will just give them indiscriminately. We are sort of in between. But, we have never had an untoward event nor do I want one.

McIntyre: What do you do when you have a positive test?

Jones: We refer them. If it's an emergency we send them out in ambulance; if not, we refer them via routine channels and follow-up to make sure they go. Now, we can't force them, you understand, but nearly all of them go to a cardiologist, either of their choice or one we suggest.

McIntyre: What do you want the cardiologist to do with them?

Jones: Well, put him on treatment. You see we are not authorized to administer treatment, so we just detect and then try to follow-up to see that the individual gets the necessary treatment.

Triebwasser: Is the patient informed of a diagnosis at that point, or do you refer them to the cardiologist as a patient having increased risk for future cardiovascular disease events?

Jones: No, we are very frank with all of our employees. Except in the presence of some psychiatric conditions, we go over the tracings with them and explain all potential implications of an abnormal test. Most of these people are scientists. They want to know. And they are very understanding and appreciative.

MEDICAL QUALIFICATION PROCEDURES FOR HAZARDOUS-DUTY AEROMEDICAL RESEARCH

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SUMMARY

Volunteer subjects have been recruited for hazardous-duty impact and vibration acceleration stress experiments during the past 10 years. Dental and lumbosacral spinal abnormalities are the major cause of disqualification. From a group of 1,277 prospective volunteers, only 63 (4.9 percent) were qualified and only 44 (3.4 percent) successfully completed the experimental program.

INTRODUCTION

Aeromedical research efforts conducted by a wide variety of military services have in common the need to properly qualify volunteers for the research. The uniqueness of military research using volunteers arises from the unusual and hazardous environments imposed by military operations and equipment. Volunteers have been used in controlled and potentially hazardous studies to measure the response to lowered atmospheric pressure, oxygen depletion, elevated temperatures, and various mechanical forces to list just a few. Usually the purpose was to determine the voluntary tolerance limits of normal healthy, young, male adults to altered and hazardous environments. The dominant concern of this military aeromedical research has been maintenance of optimal function of personnel under adverse circumstances. This is markedly different from the medical research directed toward restoring the health and function of clinically ill patients.

The purpose of this paper is to present the procedures and findings of the volunteer selection program at the Naval Aerospace Medical Research Laboratory Detachment (NAMRLD), New Orleans, Louisiana. This program began with the selection of U.S. Army enlisted personnel for impact acceleration research beginning in 1967 and prior to the establishment of NAMRLD in 1971. It has continued as the Army-Navy "Aircrew Impact Injury Protection Program" at NAMRLD using U.S. Navy enlisted personnel, and has expanded to include qualification of Navy enlisted and officer personnel for ship motion research and experienced parachutists for parachute opening shock research. Selection of volunteers for impact acceleration research has been previously reported by the U.S. Air Force (1, 2).

CATEGORIES OF VOLUNTEERS

A total of 99 volunteer subjects have been qualified for hazardous-duty experimentation between 1967 and 1977. All of these were qualified for programs in which NAMRLD, or the program preceding NAMRLD's establishment, had medical responsibility for the volunteers. The volunteers are identified by a number for each of the experimental activities, as shown in Figure 1.

Research Activity	Research Group	Volunteers by Number
Impact Acceleration	Wayne State University - U.S. Army-U.S. Navy	1 through 17
Surface effect ship motion experimentation	Naval Sea Systems Command (PMS 304)	18 through 26
Accelerations during military parachuting El Centro, CA	National Parachute Test Range and NAMRLD	27,28,54,55,68,69,91,92,98,99
Impact, vibration, and ship motion experimentation	NAMRLD	29 through 53 56 through 67 70 through 90 93 through 97

Figure 1 - Research activity, research group and identification of volunteers by number.

Volunteers #001 through #017 were U.S. Army enlisted personnel, most of them in their first tour of enlistment attached to the 28th Artillery Group, U.S. Army Air Defense Command, Selfridge Air Force Base, Michigan; others were attached to the U.S. Army Aeromedical Research Laboratory, Fort Rucker, Alabama; and two of the volunteers were flight surgeons from the Naval Aerospace Medical Institute (NAMI), Naval Aerospace and Regional Medical Center (NARMC), Pensacola, Florida.

Volunteers #018 through #026 were U.S. Navy officers and enlisted men, and one was a civilian attached to Surface Effect Ship Test Facility (SESTF), Patuxent River, Maryland. They were used in the program to determine human response to simulated surface effect ship motion.

The response of volunteers to parachute opening forces was investigated using 10 officer and enlisted U.S. Navy qualified experimental parachutists from the National Parachute Test Range, El Centro, California. The remaining group of 63 volunteers were all recruited as junior enlisted personnel from the U.S. Navy Training Command, Orlando, Florida at completion of basic training. This last group presents the major participants in the impact acceleration, ship motion, and vibration programs at NAMRLD.

RECRUITMENT OF VOLUNTEER SUBJECTS

The procedures for the recruitment of the volunteer subjects varied considerably by category, Figure 1. The largest group who underwent impact acceleration experiments consisted of 63 junior enlisted personnel who were attached to NAMRLD. Since 1974 various recruiting efforts have been utilized. Each effort utilized a bulletin board advertisement of the program at the Navy Recruit Training Command, Orlando, Florida. A presentation was made to interested recruits as a group (presentation group) after normal working hours. As a result of the presentation, those with a continuing interest were immediately interviewed (interview group). On the basis of the interview, a group was selected for screening on site (volunteer candidate group). Screening of this group was conducted within 24 hours by reviewing dental, medical, and administrative records, and by x-ray examination of the low back. Every attempt was made to eliminate those with dental or other known medical defects and those who were administratively unavailable prior to x-ray examination of the lower back. Therefore,of 241 volunteer candidates, only 137 were x-rayed. The remaining volunteer candidates reported to the Naval Aerospace Medical Research Laboratory (NAMRL), Pensacola, Florida for 2 weeks of intensive medical evaluation (evaluation group). The volunteers (volunteer group) having completed this evaluation, reported to NAMRLD, and a detailed and unique research medical record was established and is currently maintained. Volunteers arriving at NAMRLD were assigned a subject number. The nominal tour of duty is a year. Those completing their experimental protocols or remaining for a complete tour constitute the group of successful volunteers. In summary, the selection process yields a succession of groups, each one derived from the preceding group, which are:

1. Presentation
2. Interview
3. Volunteer Candidate
4. Evaluation
5. Volunteer
6. Successful Volunteer

The date of each recruitment effort and the results by group are listed in Figure 2.

Date of Presentation	Presentation Group	Interview Group	Volunteer Candidate Group	Medical Evaluation Group	Qualified Volunteer Group	Successful Volunteer Group
2/11/74	102	27	11	4	1	1
3/13/74	40	15	8	3	3	1
4/02/74	101	25	16	6	3	3
4/22/74	95	42	24	6	5	4
6/17/74	60	26	15	6	5	5
9/23/74	94	36	24	5	2	1
1/14/75	180	66	33	7	6	4
4/23/75	69	21	12	6	6	2
10/22/75	131	43	19	9	6	3
4/05/76	141	42	23	11	8	2
7/20/76	71	21	15	6	5	5
8/23/76	192	67	40	18	13	13
TOTAL	1276	431	240	87	63	44
1/17/75	1*	1*	1*			
	1277	432	241			
Percentage of Presentation Group	100%	33.8%	18.9%	6.8%	4.9%	3.4%

Figure 2 - Numerical summary of human volunteer recruitment effort at the Navy Recruit Training Command, Orlando, Florida. Each group is derived from group to left.
* One individual was identified separately from the usual recruitment procedures.

The Army enlisted volunteers were recruited in 1967 and 1968 by circular or verbal advertisement to their parent command. They were the first group of volunteers used in this program, and they were used exclusively for impact acceleration research. Each potential volunteer was given a detailed explanation of the impact acceleration levels to be evaluated during the program. For illustration, a film of human impact acceleration study conducted at the U.S. Naval Air Crew Equipment Laboratory, Philadelphia, Pennsylvania was shown. The film depicted the type of experimental arrangement and equipment to be used, and clearly illustrated the amount of movement of the human head and neck that can occur with no injurious effects. Persons desiring to participate in the program after the above proceedings were accepted provided that they completed the thorough examination as described below. This effort resulted in identifying a total of 38 volunteer candidates in November 1967 and September 1968. From these, 15 subjects, #003 through #017, were qualified and completed their series of experiments with the exception of one individual who withdrew. Subjects #001 and #002 were U.S. Navy Flight Surgeons assigned to the research staff. The subsequent recruitment program for Navy volunteers evolved from this experience.

The SESTF volunteers, #018 through #026 (Figure 1), were recruited by their parent command. A group of 13 volunteer candidates was originally sent for medical evaluation and 9 were considered qualified and successfully used.

The eight experimental parachutists who also qualified as volunteers for biomedical research involving parachute jumps were recruited by their parent command. Although all were qualified for their parachutist activities, they were not necessarily qualified for biomechanical research at NAMRLD. This discrimination resulted because the experimental design compared dynamic data from volunteers undergoing opening shock in parachute jumps with dynamic data from impact acceleration experiments at NAMRLD on the same volunteer. Those volunteers willing and qualified could participate in both programs.

QUALIFICATION OF VOLUNTEER SUBJECTS

The volunteer subjects were recruited, evaluated, and used in strict accordance with procedures specified in SECNAVINST 3900.39, Subj: Use of volunteers as subjects in research, development, test and evaluation, 28 April 1969. They perform duty as experimental subjects (3, 4, 5, 6, 7, 8, 9, 10, 11, 12), utilizing experimental acceleration or deceleration devices. Since all the experimental protocols call for the use of such experimental devices, the subjects were qualified for hazardous-duty pay under the provisions of United States Public Law. The detailed medical qualification of each individual subject therefore assumes paramount importance. These qualifications are considerably more stringent than the normal medical qualifications for military service or for various other categories of experimental stress duty. In effect, each particular subject must be free of any defect that would increase his susceptibility to injury under the specified experimental stress, before the subject is ever used in an experiment.

There have been modifications to the medical examination protocol as a result of experience and changes in capability that have occurred since 1967 when the first Army volunteers were qualified. The following protocol is the one used in evaluating the 63 Naval recruits attached to permanent duty at NAMRLD, and has been used since 1974.

This examination is conducted by the staff of NARMC, NAMI, and NAMRL, Pensacola, Florida. It is organized according to specialty consultations. The consultations required are as follows:

1. Dental evaluation, with full x-ray examination of all teeth to determine the quality of bite, the status of each individual tooth, and its root structure. This is required in order to determine that there is an adequate dental, gingival, and bony base to support the specialized anatomical mount that holds the inertial instrumentation used in the experiments.

2. Internal medicine examination by a board qualified specialist. This includes:
   (a) Standard 12 lead electrocardiogram with the volunteer fasting and rested.
   (b) Exercise electrocardiogram according to the Bruce protocol (13).
   (c) Vectocardiogram, utilizing the Frank lead system (14).
   (d) Echocardiogram in cases of heart murmur.
   (e) Pulmonary function studies with determination of forced expiratory volume (FEV), forced expiratory volume in one second (FEV1), percentage ratio of FEV to vital capacity (VC), maximum expiratory flow rate (MEFR), maximum mid expiratory flow rate (MMEFR), and maximum voluntary ventilation (MVV). A standardization group is available (15).
   (f) Blood chemistries using the SMA-19 profile which includes calcium, inorganic phosphate, glucose, blood urea nitrogen (BUN), uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, lactic dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT), sodium, potassium, chloride, carbon dioxide combining power (CO_2) creatinine, serum iron, triglyceride, and 2 hour post prandial blood sugar. In addition, the beta, pre beta, and alpha lipoprotein fractions are determined in selected cases.
   (g) Hemogram, which includes hemoglobin (Hgb), hematocrit (Hct), red blood cell count (RBC), total white blood cell count (WBC), differential WBC, platelet count, prothrombin time (Protime), and partial thromboplastin time (PTT).
   (h) Urinalysis, which includes appearance, specific gravity, pH, protein, glucose, acetone, occult blood, and microscopic examination of the urinary sediment after centrifugation.

3. Electroencephalographic examination with interpretation by a neurologist. The examination includes an effort to elicit latent seizure activity by hyperventilation and/or photic driving.

4. Ophthalmological examination under the supervision of a board qualified specialist. Visual acuity, manifest refraction, tonometry in indicated cases, and visual fields with the Goldman perimeter are recorded. Five photographic views of each fundus, centered on the optic disc, are obtained.

5. Musculoskeletal examination by a board qualified orthopedic surgeon including review of the x-rays of the skull and of the entire vertebral column.

6. Ear, nose, and throat examination by a board qualified specialist with indirect laryngoscopy. Any variation of airway structure is carefully evaluated. The external auditory canals are examined and cleansed prior to audiometric examination.

7. Detailed audiological examination by the Acoustical Sciences Division, NAMRL. The tests conducted are pure tone audiogram, speech audiometry, and tone decay test.

8. Psychological evaluation by the Personnel Research Division, NAMRL. The specific personality tests employed are the Guilford-Zimmerman Temperament Survey, Eysenck Personality Inventory, and the Taylor Modified Anxiety Scale.

9. Psychiatric consultation and interview by a board qualified psychiatrist or a clinical psychologist under his supervision. In addition to a standard clinical psychiatric interview, the Bender-Gestalt test, the Minnesota Multiphasic Personality Inventory (MMPI), and the Graham-Kendall Memory for Design Test are administered to each candidate.

10. Ataxia testing is performed using a rail test battery of: walk-3/4"-wide-rail-eyes-open (walk E/O), stand-on-3/4"-wide-rail-eyes-open (Stand E/O), stand-on-2¼"-wide-rail-eyes-closed (Stand E/C), and a floor test battery of: sharpened Romberg (SR), stand-one-leg-eyes-closed (SOLEC R&L), walk-on-floor-eyes-closed (WOFEC). These tests and results of the standardization group are described (16, 17, 18).

11. Detailed consultation by the Perceptual and Behavioral Sciences Division, NAMRL, for the purposes of specific testing of the vestibular system. Several examinations are administered over a period of days, and are as follows: a quantitative form of sensation cupulometry using the periodic angular rotator device (PAR), a quantitative measure of nystagmus using the human disorientation device (HDD), a test of nystagmus possibly related to otolith function (PATE), the visual vestibular interaction (VVI) test, the brief vestibular disorientation test (BVDT), and dynamic visual acuity (DVA). Detailed description of each test and partial standardization group data are available (19, 20, 21, 22, 23, 24). The results of the VVI, BVDT, MSQ, and PATE are used in an attempt to rank susceptibility to motion sickness.

12. Additional vestibular function testing is performed by the Physiological Optics Division, NAMRL. The counter-rolling index, oculogyral illusion, cold and hot caloric threshold, and Fitzgerald-Hallpike scores are developed from the tests. Description and application of the tests are available (25,26,27,28).

13. X-ray examinations are as listed:

(a) Posterior-anterior (P-A), anterior-posterior (A-P), right and left lateral of skull, and open mouth odontoid process view.

(b) A-P lateral, left and right oblique, hyperextension and hyperflexion of cervical spine.

(c) A-P chest.

(d) A-P and lateral thoracic spine.

(e) A-P standing, recumbent lateral, left and right oblique of lumbosacral spine, and coned down view of the lumbosacral junction.

In this series of detailed examinations, each abnormality identified is carefully documented. A judgment is made concerning the significance of this abnormality with regard to the fitness of each volunteer candidate. In individual cases further medical consultations may have been required. Also when a candidate is found to have a disqualifying problem, subsequent parts of the medical evaluation are often cancelled, thus resulting in an incomplete examination.

Subjects #001 through #017 were qualified by using the same categories of specialty examinations at Pensacola, Florida as described above. The group from which subjects #008 through #017 were qualified was evaluated at Lyster Army Hospital, Ft. Rucker, Alabama, in addition to the specialty examinations at NARMC, NAMI, and NAMRL, Pensacola, Florida. However, there were significant differences in certain test procedures. A barium swallow cardiac series was used for the group from which #003 through #007 were qualified. Echocardiograms were not available. Ballistocardiograms and tilt table tests were also administered. A clinical neurological examination, which is not done currently except on request by one of the other specialty examiners, was done. Additional tests of vestibular function have been added as they have been developed at NAMRL, Pensacola, Florida.

Subjects #018 through #026, plus the 10 parachutists, were not screened by the psychiatric consultant because of proven personality stability evident from their service experience. Otherwise their examinations were identical to those for the 63 Naval recruits assigned to NAMRLD.

RESULTS

The volunteers, from which subjects #003 through #017 were qualified, were recruited at separate times. The first group, subjects #003 through #007, was qualified from a list of 22 volunteer candidates identified November 21, 1967. The defects of those disqualified are listed in Figure 3. The classification system for categorizing defects was adopted from "Standard Nomenclature of Diseases and Operations" (29). (Note: The topographical classification was used with the addition of the categories dental, administrative, extraneous, and withdrew.) Six were disqualified for unspecified reasons, presumably voluntary withdrawals. Four were disqualified due to dental defects of various types. Three candidates had disqualifying musculoskeletal anomalies. One had bilateral spondylolysis, and another had an old fracture of the sixth cervical vertebra. The third had sacralization of the fifth lumbar vertebra and cervical osteoarthritis. This last subject also had an abnormal electroencephalogram. The other four subjects were disqualified because of:

1. Significant cardiac murmur.
2. History of hematuria.
3. History of concussion.
4. Excessive myopia.

This yields a qualification rate of 23 percent of the volunteer candidates. One withdrew prior to significant experimentation, thus yielding four successful volunteers.

SYSTEM	
Musculoskeletal	3
Cardiovascular	1
Dental	4
Urogenital	1
Nervous	2
Eye	1
Unspecified (Presumed voluntary withdrawals)	6

Figure 3 - Disqualifying defects by system of Army voluntary candidates from which #003 through #007 were qualified. One candidate had disqualifying defects classified in two systems.

Ten volunteers, #008 through #017, were selected from a volunteer candidate group of 16 individuals in September and October 1968. The cause for disqualification of the six individuals is unknown. All of the qualified volunteers successfully completed the experimental program.

The 9 subjects, #018 through #026, were qualified from 13 volunteer candidates nominated from SESTF personnel. The four disqualified candidates and their disqualifying conditions were:

1. Candidate 1, goiter.
2. Candidate 2, hypertension.
3. Candidate 3, cardiomyopathy.
4. Candidate 4, history of recurrent renal calculus disease.

When candidate 1 was examined by the internist, he was found to have a previously undetected enlarged thyroid. Although he appeared clinically euthyroid, the presence of this significant unexplained abnormality required certain specialized studies in order to establish the etiology of the goiter. After the examination at Pensacola, Florida was terminated, the candidate was disqualified, and was returned to his command with the recommendation that definitive thyroid studies be undertaken. After the appropriate investigations, candidate 1 was found to be euthyroid and his condition was diagnosed as simple, non-toxic goiter. Candidate 2 was found to have a history of significant hypertension with a previously reported elevation of vanilmandelic acid (VMA) and catecholamines from a 24-hour urine specimen. He was hospitalized at the National Naval Medical Center, Bethesda, Maryland, for evaluation of the elevated blood pressure and abnormal urine chemistries. No evidence of pheochromocytoma was found, and his condition was ultimately diagnosed as benign essential hypertension. Candidate 3 was felt to have an early cardiomyopathy of uncertain etiology. Pertinent physical findings consisted of a third sound, demonstrated by phonocardiography. There was no evidence of cardiac decompensation. The examining internist felt that he should not be subjected to the stress of motion experiments. He was disqualified and counseled as to the nature of his condition. No further studies were recommended. Candidate 4 was found to have a history of renal calculus disease, documented by two hospital admissions for flank pain and hematuria, and additionally by one episode of passing a calculus while urinating, accompanied by hematuria. Renal calculus disease is suspected to be aggravated by vibration (30) and thus candidate 4 was disqualified. No further studies were recommended.

There were 240 volunteer candidates identified at the Naval Recruit Training Command, Orlando Florida. Of this group, 153 were disqualified at Orlando based on a brief interview, lumbosacral spine x-rays, review of dental records, and review of service records with the results listed in Figure 4. Three individuals had multiple reasons for being unacceptable. One had musculoskeletal defects and voluntarily withdrew. It should be noted that not all of the 240 volunteer candidates at Orlando had x-ray examinations of the low back. Every attempt was made to identify those with dental defects and administrative conflicts prior to undergoing x-ray examination. Only 136 volunteer candidates underwent lumbosacral spine x-rays at Orlando. In addition, one candidate ordered to NAMRLD in error underwent lumbosacral x-rays, making a total of 137, Figure 5.

Condition	Number of Candidates Disqualified at Orlando	Percentage
Dental	53	22.1%
Administrative	38	15.8%
Extraneous	5	2.1%
Musculoskeletal	29	12.1%
Withdrew	25	10.4%
	150	
Multiple	3	
	153	

Figure 4 - Causes and rates of disqualification among the 240 volunteer candidates at the Naval Recruit Training Command, Orlando, Florida.

The category of musculoskeletal defects is the most interesting. Most defects involved the low back area and were evident on x-ray. There were 31 individuals disqualified because of low back problems identified at Orlando. Three of these had spina bifida occulta (SBO), usually of the first sacral vertebra (S_1), and were disqualified in 1974. After review of the literature and extensive consultation, it was decided to accept individuals with SBO provided that it was limited to the fifth lumbar vertebra (L_5) or S_1, that it was small, and was not associated with a history or physical findings to suggest neurological involvement (31). Therefore, under current criteria, these three would not be disqualified. Fourteen had spondylolysis with or without spondylolisthesis. Nine had lumbarization of S_1 or sacralization of L_5. Six had abnormal and excessive scoliosis including one who also had spondylolysis. One had vertebral osteochondrosis and also spondylolysis. Another one had a history of neck injury with persistent symptoms thus bringing the total to 32 individuals, who were identified and disqualified at Orlando with musculoskeletal defects. Additionally, there were three more cases of spondylolysis, one case of lumbarization of S_1, and one case of vertebral osteochondrosis diagnosed after examination in Pensacola. One case of lumbarization was accepted and used as a volunteer. Another case of excessive scoliosis was disqualified at New Orleans shortly after acceptance. The rates for these four conditions in the 137 individuals evaluated with low back x-rays are given in Figure 5. None of these individuals would be considered disqualified for military service unless they had symptoms associated with the physical findings.

	Orlando	Pensacola	After Acceptance	Total	Percentage
Spondylolysis	14	3	0	17	12.4%
Lumbarization/sacralization	9	1	1	11	8.0%
Excessive Scoliosis	6	0	1	7	5.1%
Other	1	1	0	2	1.5%

Figure 5 - The cases and overall rate of disqualifying defects observed on lumbosacral x-rays of 137 Naval recruit volunteer candidates for hazardous-duty research. Two volunteer candidates had two disqualifying defects. Three candidates, disqualified because of SBO, are not included.

The dental criteria for acceptance as a volunteer candidate were unusually high, because of the requirement to form a stainless steel casting of the hard palate and maxillary teeth. This casting is used as a platform for inertial instrumentation during impact acceleration experiments (5). All volunteer candidates with multiple maxillary extractions, periodontal disease, unfilled caries requiring more than simple restoration, and malocclusion that would interfere with the impression procedure were disqualified. Due to the excellent records available on the recruits, this review was easily done in Orlando. Twenty-two percent of the 240 volunteer candidates were dentally disqualified at Orlando prior to being sent to Pensacola for definitive medical evaluation. Also, it was possible to construct a steel mouth mount on every qualified subject, and once a subject was qualified, he was never lost from the program because of dental reasons.

Administrative losses were limited to those who were enrolled in Navy training programs that precluded the time for them to spend a year at NAMRLD as a volunteer, or individuals who were judged unsuitable based on review of their service record. The extraneous category included only those known to have used unauthorized drugs.

Twenty-four of eighty-seven individuals were disqualified in Pensacola for a wide variety of reasons, with 35 disqualifying defects listed in Figure 6. Since the policy was to terminate the examination as soon as a disqualifying defect was found, it is possible that other undetected problems existed in a disqualified subject but were not detected. The major category of disqualifying defects is musculoskeletal, despite the effort to rule out all cases of lumbosacral spinal defects before reporting to Pensacola. These included three cases of spondylolysis including one with spondylolisthesis and one case of lumbarization of S_1. It is obvious that these were missed during the examination in Orlando and are mentioned in the above paragraph, Figure 5. There were four other individuals with miscellaneous musculoskeletal defects.

Psychiatric	7
Integumentary	0
Musculoskeletal	8
Respiratory	4
Cardiovascular	2
Hemic-Lymphatic	1
Digestive	1
Dental	0
Urogenital	0
Endocrine	1
Metabolic/Biochemical	0
Nervous	4
Eye	1
Ear	1
Administrative	0
Extraneous	3
Withdrew	2

Figure 6 - The disqualifying defects of the 24 individuals disqualified during intensive medical evaluation at Pensacola, Florida, tabulated by system.

The second major group of disqualifying defects was psychiatric, and due primarily to behavioral and situational disorders such as alcoholism, depression, or anxiety reaction associated with military service. A diagnosis of psychosis or neurosis was never made. The nervous system defects were due to mildly abnormal electroencephalograms without clinical diagnosis. The other disqualifying defects were distributed among the various systems.

In addition to finding disqualifying defects, it is also necessary to identify non-disqualifying defects on volunteers. Virtually every qualified candidate had minor defects requiring documentation and evaluation, and usually he had more than one such defect. Non-disqualifying defects are summarized for the 15 Army volunteer subjects #003 through #017 in Figure 7. Of the 15 volunteers, 2 had no defects, 3 had one defect, 5 had two defects, 4 had three defects, and 1 had four defects. Again the musculoskeletal category was the most prevalent with eight individuals manifesting musculoskeletal defects. One had a lumbarization of S_1 and an old compression fracture of the eighth thoracic vertebra (T_8) with wedging. Another had sacralization of L_5. A third had dorsal displacement of L_5 on S_1. These three volunteers would be considered disqualified by current standards. A case of spina bifida occulta of L_5 and a case of Schmorl's node of the superior surface of L_2 were accepted and would also be accepted at this time. However, at one point during the program, such cases were disqualified. The other cases of non-disqualifying defects of concern were two cases of persistent or intermittent elevated diastolic blood pressure and three individuals with borderline elevated diastolic blood pressure and three individuals with borderline elevated 2-hour post prandial blood sugar. Most of the eye and ear problems were refraction errors and minimal high frequency hearing loss. The other defects were miscellaneous and incidental.

SYSTEM	
Psychiatric	1
Integumentary	0
Musculoskeletal	8
Respiratory	1
Cardiovascular	2
Hemic-Lymphatic	2
Digestive	0
Dental	0
Urogenital	3
Endocrine	0
Metabolic/Biochemical	4
Nervous	0
Eye	4
Ear	3
Vestibular	1

Figure 7 - Non-disqualifying defects of 15 qualified U.S. Army volunteers, #003 through #017.

Of the 13 SESTF candidates who were evaluated, 9 were qualified, and 4 were disqualified. The medical defects of the qualified candidates are listed in Figure 8. Three categories of defects are prevalent; the percentage of qualified volunteers with common defects in these three categories are:

1. Defective visual acuity (55%).
2. Mild hearing loss (33%).
3. SBO (33%).

SYSTEM	
Psychiatric	0
Integumentary	0
Musculoskeletal	5
Respiratory	3
Cardiovascular	2
Hemic-Lymphatic	1
Digestive	0
Dental	0
Urogenital	1
Endocrine	0
Metabolic/Biochemical	1
Nervous	0
Eye	4
Ear	4
Vestibular	0

Figure 8 - Non-disqualifying defects on nine qualified Surface Effect Ship Test Facility crew members.

The rate of SBO is consistent with our previous experience in qualifying human volunteers for impact acceleration experiments. Since the spinal defect was minimal and the planned simulations were thought not to impose a major stress on the vertebral column, the subjects with SBO were qualified. Subject #020 indicated an abnormal 2-hour post prandial blood sugar. However, follow-up studies revealed no abnormality which could be definitively termed "diabetes mellitus," and therefore he was eventually qualified to participate in the motion study. Subject #026 was found to have congenital hereditary spherocytosis previously treated by splenectomy. He was found to have normal hemoglobin levels, complete remission of symptoms, was considered to be in good health, and hence not an excess risk.

There were 63 Navy recruits qualified as volunteers for hazardous-duty biomechanical experimentation. As in the case of other groups of volunteers, almost every volunteer had one or more notable, non-disqualifying defects. The defects within each system are tabulated in Figure 9. If an individual had multiple defects within a system, only a single entry is made. There were 195 defects by system for the 63 volunteers. Musculoskeletal defects were present in 34 individuals. Twenty-one individuals had a mild degree of scoliosis, but it was not considered disqualifying. Another one had sufficient scoliosis of the lumbar spine and kyphosis of the cervical spine that he was disqualified after acceptance. One subject with lumbarization of S_1 completed the experimental protocol but should have been disqualified, Figure 5. Another subject with hypoplastic neural arch of C_1 completed the experimental program but should also have been disqualified. Seven subjects had spina bifida occulta of L_5 or S_1. The remaining musculoskeletal problems were highly variable and incidental.

Most of the 24 individuals with eye abnormalities had refractive errors, phorias, or tropias. Most of the 28 individuals with ear problems had high frequency hearing loss. The 12 with vestibular non-disqualifying defects had abnormal ataxia or vestibular physiology test results on one or more tests without confirmation of a clinical abnormality.

Of the 24 individuals with non-disqualifying respiratory defects, only 3 had abnormal pulmonary function tests, and they were all of the obstructive type. All the other individuals had either nasal septal deviation, allergic rhinitis, or incidental hypertrophic changes noted on sinus x-rays.

There were 17 individuals with metabolic/biochemical abnormalities which consisted of one or more abnormal blood chemistry determinations. No clinical diagnosis was rendered even after careful evaluation of the biochemical anomalies.

There were 23 individuals with non-disqualifying defects of the cardiovascular system. Sixteen individuals had "benign" systolic ejection murmurs. Recently it has been decided to evaluate all such murmurs with echocardiography because of the possibility that minor structural changes to the mitral and/or aortic valves could account for the murmurs. Information on this effort is not yet available. Six volunteers had non-pathological variations of rate or rhythm in the either the standard electrocardiogram or the vectorcardiogram. One had a saphenous vein stripping for unknown reasons.

The other categories of non-disqualifying defects had a low frequency of occurrence. These were incidental problems and although classified by system, they were etiologically disparate. The hemic-lymphatic defects were due to benign hypertrophy of lymphatic tissue or abnormalities of the hemogram which were without clinical importance.

SYSTEM	
Psychiatric	9
Integumentary	6
Musculoskeletal	34
Respiratory	24
Cardiovascular	23
Hemic-Lymphatic	10
Digestive	3
Dental	1
Urogenital	3
Endocrine	0
Metabolic/Biochemical	17
Nervous	1
Eye	24
Ear	28
Vestibular	12
TOTAL	195

Figure 9 - Non-disqualifying defects of 63 U.S. Navy recruit volunteers.

It is possible to derive estimates of the prevalence of low back anomalies among all the volunteer candidates from the four sources, Figure 1, based on x-ray evaluation. Twenty-three individuals had lumbosacral spine x-rays in the groups from which subjects #001 through #017 were qualified. Thirteen SESTF personnel and ten parachutists had lumbosacral spine x-rays. There were 137 Naval recruits who were x-rayed, from which 63 were ultimately qualified. The total number receiving lumbosacral spine x-rays was 183.

Four categories of disqualifying lumbosacral spine defects are listed in Figure 10. The category "cervical spine" includes seven cases of miscellaneous disqualifying cervical vertebral spine defects. These were detected on individuals who were further evaluated after lumbosacral spine x-rays usually with full vertebral spine x-rays. Therefore, no rate of cervical spine defects within the group of 183 volunteers is given since most did not have cervical spine x-rays.

Spondylolysis	20	10.9%
Sacralization/Lumbarization	14	7.7%
Excessive Scoliosis	6	3.3%
Vertebral Osteochondrosis	2	1.1%
Cervical Spine	7	
Individuals with Disqualifying Defects of the Spine	46	

Figure 10 - Disqualifying defects and rates of the vertebral spine on 183 individuals undergoing lumbosacral x-rays. Three individuals had two disqualifying defects. No rate is given for cervical spine defects since not all 183 individuals underwent cervical spine x-rays.

The same analysis for non-disqualifying vertebral spine defects is presented in Figure 11. Most of these 71 individuals had full vertebral spine x-rays in addition to the lumbosacral spine x-rays. Defects other than in the lumbosacral spine are listed without a rate because all 183 individuals did not have full vertebral spine x-rays.

There were 12 individuals with both disqualifying and non-disqualifying defects, and are therefore entered in both Figures 10 and 11. Accounting for these, there are 105 individuals with one or more documented defects of the vertebral spine evident on x-ray. Six of these had non-disqualifying cervical spine defects and lumbosacral spine anomalies. Four had non-disqualifying defects of the spine not located in the lumbosacral area. Therefore, 95 (52 percent) of 183 individuals had lumbosacral spine anomalies detectable by x-ray. There were 40 (22 percent) of 183 individuals who had disqualifying lumbosacral spine defects, and an additional 55 (30 percent) of 183 had non-disqualifying lumbosacral spine defects.

Spina Bifida Occulta	31	16.9%
Schmorl's Nodes	11	6.0%
Mild Scoliosis	30	16.4%
Other/Lumbosacral Spine	4	2.2%
Other/Non-Lumbosacral Spine	5	
Individuals with Non-Disqualifying Vertebral Spine Defects	71	

Figure 11 - Non-disqualifying lumbosacral spine defects and rates on 183 individuals undergoing lumbosacral spine x-rays. Eight individuals had two non-disqualifying defects and one had three. For explanation of other non-lumbosacral spine, refer to text.

The screening program which concentrates on rapidly removing those with dental and low back defects is highly effective in selecting subjects for hazardous-duty, biomechanical research. Those with administrative conflicts are losses characteristic of our recruitment constraints and experience and have no general applicability. The protracted and detailed medical evaluation is essential to identify the residual 24 of 87 volunteer candidates who are unacceptable. There is no easy way to identify this last group because there is no clustering of the types of defects found at this stage of the evaluation process.

Even after presentation, interview screening, and medical evaluation, 19 of 63 qualified volunteers did not successfully complete the program. Twelve volunteers were lost due to the unauthorized use of drugs, and this could not have been predicted in any way. Recent experience with losses due to this cause has been improved by emphasis throughout the recruitment program that unauthorized use of drugs is destructive to this research and those using them should not apply. The remaining seven volunteers were lost for a variety of unpredictable reasons.

DISCUSSION

The x-ray examination of volunteer candidates for research since 1966 has uncovered four major anomalies of the low back in a large percentage of the volunteer candidates. The anomalies are 1) spina bifida occulta (SBO), 2) lumbarization of the first sacral vertebra or sacralization of the first lumbar vertebra, 3) spondylolysis with or without spondylolisthesis, and 4) Schmorl's nodes. The literature regarding these four lesions is confusing. The implications of the lesions are highly variable with no consistent agreement on what the prognosis is. One consistent fact about these lesions is that they are very prevalent in any population, and they are highly variable in the specific anatomical presentation of each lesion. Speaking from a critical point of view, none of these are taken very seriously, except in those cases where there are specific clinical signs associated with the lesion which cannot be attributed to any other abnormality or anomaly of the low back area. However, when these anomalies are present in individuals otherwise free of symptoms, there are no estimates on what percentage of subjects might subsequently develop symptoms associated with these lesions. In particular, there are no estimates on what percentage of subjects would be expected to have symptoms associated with these findings under stress testing of impact or vibration. Discussion of the selection problem with different orthopedic surgeons will yield different views ranging from the judgment that none of these subjects should be selected to the opinion that all of the subjects should be selected, provided they have no associated clinical findings. A review of each of the anomalies in turn and an attempt to summarize the critical parts of the literature follows.

Epstein (32) summarizes the incidence of spina bifida occulta. He describes the anomalies as a cleft spinous process. The mildest form is a lack of fusion of the neural arches of one or several vertebrae. The most common locations are at the fifth lumbar and the first and second sacral arches. He summarizes the results from several authors; Southworth and Bersack (33), who reported that out of 550 patients with anomalies of the lumbosacral vertebrae, most had little or no symptoms referable to the low back. Spina bifida occulta was present in 18.2 percent. Dittrich (34) reported that 5 percent of all spines examined roentgenographically showed spina bifida occulta. Breck, Hillsman, and Basom (35) reported an incidence of 6 percent in the series of 450 cases. Particularly interesting is the report by Friedman, Fischer, and Van Demark (36), giving an incidence of 36 cases of spina bifida occulta in a review of 100 soldiers. Epstein agrees that the last is the best estimate of the prevalence of SBO. We found 16 percent of our volunteer candidates with this anomaly. In terms of development, Epstein points out that the laminae fuse at about the first year of life, and the development is completed during adolescence and hence the cleft spinous process seen at the end of adolescence should remain throughout life. Epstein reviews the clinical implications of SBO with the statement "while most patients with lumbar cleft spinous process usually have no specific complaints, there are certain cases in which the anomaly may be accompanied by low back pain. Such cases are very difficult to evaluate. The defect should not be held as the responsible factor until all the possibilities have been excluded." He then alludes to a series of cases by Jelsma and Ploetner (37) who reported a group of 18 patients with low back pain radiating to the hips and sometimes to both lower extremities or to one leg, wherein surgery disclosed a mass of fibrous or fibrolipomatous tissue often with a constricting mass of fibrous tissue involving the dura. A traction mechanism caused by the fibrous tissue connection from the dura through the cleft to the lumbar fascia is the explanation of the pain. There is corroboration of Epstein's review of these 18 cases by James and Lassman (38). They point out that there is a gradation from

spina bifida occulta to spina bifida aperta which involves herniation of the meninges outside of the vertebral canal through the spinal defect. Their cases were differentiated by surgical exploration. The fact that abnormal traction can be exerted on the dura at the point of the spina bifida occulta appears to be established. Schmorl and Junghanns (31) give a slightly different presentation of the problem of spina bifida occulta. They point out that cleft formation is the most common malformation of the vertebral arches. They qualify the significance of these clefts by the general statement that only the smallest of the vertebral clefts, for example individual smooth edge small clefts of the spinous processes, can be considered as insignificant. Such a cleft may be seen and diagnosed as SBO from the x-ray. They also point out that clefts can occur on different parts of the arch including the pars interarticularis, the pedicle, and the border between the pedicle and the vertebral body. We are seeing the clefts of SBO in our volunteers. Clefts of the pars interarticularis are seen and diagnosed as spondylolysis. Clefts in other areas have not been noted in our subjects. *Hintze (39) found clefts in early childhood in 100 percent of all humans. At age five the number decreased to 81 percent, the 15th year to 44 percent, and the 50th year to 10 percent.* In the case of our subjects, between the ages of 18 and 21, an occurrence of 30 to 40 percent is consistent with these findings. They indicate that most of these malformations are insignificant and do not cause pain. However, if they are associated with the anomalies of the spinal cord and their membranes, they may present difficulties in some exceptional cases and there may be serious consequences. These various references pertaining to spina bifida occulta indicate that the importance of the lesion has to be discerned through the clinical history and clinical findings rather than any of the x-ray findings. Without these clinical findings, the x-ray findings are considered incidental. However, nobody makes any attempt to determine what the probability of future symptoms is in a person who has the incidental finding on x-ray, or what the significance of these lesions is from the point of view of stress either from occupation or experimentation. Therefore, we accept volunteer candidates with small clefts of L_5, S_1, or S_2 provided that they are free of any history of back pain. However, it is conceivable that the stress testing these subjects are undergoing, could elicit symptoms which otherwise would never be seen.

The findings of lumbarization of S_1 or sacralization of L_5 are usually considered as malformations of the lumbosacral junction. The malformations can take a myriad of forms. Basically, the problem is describing what the articulation between the transverse process of the affected vertebra and the sacrum is. This articulation can vary from a completely calcified strut with no motion possible, to a partial joint, to a thin fibrous attachment. The lesions may be asymmetrical from the left or from the right. The various possibilities of these anomalies are described by Epstein (32). He qualifies these anomalies by the statement, "The structure of the transverse processes of the fifth lumbar and the first sacral segments often is of considerable interest particularly if articulations are formed between the tips of the transverse processes of the fifth lumbar vertebra and the adjacent sacrum and illiac bones. It is generally believed that if this change is bilateral, no weakening of the lumbosacral articulation exists. However, if it should be unilateral, changes in stress may result in painful syndromes and arthritic manifestations may occur. In my own experience such changes have often been observed in patients who had no symptoms whatsoever. Unless examination failed to disclose any other reason for pain in the lumbosacral region, I would hesitate before deciding that the existence of such anatomical variation is a definitive cause for the patients' complaint." Schmorl and Junghanns (31) also comment on these transitional vertebra which can be either a lumbarized first sacral vertebra or a sacralized fifth lumbar vertebra and make an important point that the exact nature of the lumbosacral transitional vertebra can only be determined after an exact count of the total number of vertebral bodies. The actual prevalence of the transitional lumbosacral vertebra varies from 0.6 to 25 percent which is consistent with the prevalence in our volunteer candidates at *8 percent. The authors discuss the implication of a transitional lumbar vertebra in that the presence of the transitional* vertebra in itself does not cause pain. The source of pain seems to be secondary to the arthrosis of newly formed articulations between the enlarged transverse process and the wings of the sacrum with inflammation of the bursae and perhaps periostitis. They come to the same conclusion as Epstein in the sense that if no other cause for pain has been found, therapy should be concentrated at the transitional vertebra. In any case, from the clinical point of view, these findings are of no concern unless the patient has symptoms. As in the case of spina bifida occulta, there are no series of cases which have been collected for a prospective study of the subsequent development of symptoms; also there are no series of cases wherein predictions have been made of the relationship between the occurrence of the x-ray picture and the onset of symptoms due to stress, particularly to structural stress of impact and vibration acceleration. From the point of view of pre-employment consideration of these anomalies, Barton and Biram (40) found 856 defects in 498 patients in 1000 consecutive preplacement examinations and concluded that spondylolysis, spondylolisthesis, arthritis, and in some cases, transitional lumbosacral vertebrae were significant factors in back strain in workers over 45 years of age. They find that the incidence of chronic low back pain due to physical exertion might be minimized by the avoidance of undue strain in individuals who appear to be susceptible to such disturbances by reason of an anatomic variation in their spine. These series would indicate that from the prognostic or the prospective point of view most occupational medicine examiners would take a conservative approach to the utilization of people with transitional vertebrae and spondylolisthesis. Therefore, we have elected to exclude volunteer candidates with transitional vertebrae or with spondylolysis, with or without spondylolisthesis.

Schmorl and Junghanns (31) report the occurrence of Schmorl's nodes in association with congenital factors and as degenerative changes associated with ordinary stress and with trauma. The node is an intrusion of the nucleus pulposus through the end plate of the vertebral body into the substance of the vertebral body, with the characteristic x-ray picture. For the purpose of x-ray examination of volunteer subjects, it is absolutely essential to document any such nodes in order to avoid the situation where it could be claimed that the acceleration stress resulted in the formation of the node. As usual there are no series clearly indicating what the prognostic or prospective clinical significance of these nodes is with regard to the strength of the vertebral column, the individual vertebral bodies, or the intervertebral discs. Schmorl reported a frequency of 38 percent of all spines examined. We found only 6 percent. However, when radiologically determined, the frequency is only about 13.5 percent as determined by Schmorl. The discrepancy is due to the fact that anatomically demonstrable nodes are not necessarily seen on x-ray. Epstein (32) describes the mechanism of occurrence of Schmorl's nodes as a prolapse of the nucleus pulposus into the vertebral body. However, for definitive consideration of the problem of Schmorl's nodes and their *relationship* to alterations of the intervertebral discs, Epstein refers agin to the monograph by Schmorl and Junghanns (31). In any case, the nodes are an indication of prior defect and appear to be of no prognostic importance, because any commentary about subsequent difficulties arising from the existence of these nodes is lacking. In the case of our subjects, when the lesion has been described by either the radiologist or the orthopedic surgeon, it has been considered an incidental finding. Epstein (32) shows a case of an athletic, young female with multiple Schmorl's nodes involving many vertebrae who was completely asymptomatic.

CONCLUSIONS

The conduct of hazardous-duty impact and vibration acceleration stress experiments requires access to large numbers of prospective volunteers. From 1,277 individuals, 241 volunteered, 63 were qualified, and 44 successfully completed the experiments. Despite a young, healthy,adult male polulation between 18 and 25 years of age, the majority of volunteers were disqualified because of dental and lumbosacral spine defects. Extremely detailed medical examinations were required to identify those individuals with widely disparate disqualifying medical defects. Such a detailed examination is also required to develop a detailed baseline of non-disqualifying defects prior to experimentation.

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DISCUSSION

Clement: Perhaps you have already mentioned it, but what do you call excessive scoliosis?

Thomas: Excessive scoliosis are those cases judged by the orthopedic surgeon and the research medical officers, to constitute a potential threat. This cannot be quantified and is based on a review of the x-rays by the consultants. There were no numerical criteria used in terms of the degree of scoliosis.

Lequay: Don't you think that a standard set of criteria for elimination because of the spine is very important? We have the same problem in France, and we have been forced to modify the norms for the interpretation of our x-rays. Presently, the degree of the scoliosis causing elimination is 25 degrees. What is your opinion of this method of elimination?

Thomas: You must keep in mind the purpose of our examinations is to qualify individuals for an experimental program, on which there is a tremendous responsibility on the part of the medical research staff to identify people that would be at excess risk because of any defect they might have. It is a far more stringent research requirement than that used to qualify people for any occupation. Now in the case of 25 degrees of scoliosis, on the review of the cases I'm sure we would have disqualified all of them for impact acceleration research. We probably would have disqualified individuals having a lesser degree of scoliosis. Many of the cases of scoliosis that were disqualified were disqualified on the basis that they had secondary curves, not just one area of scoliosis. They would have a series of convexities or concavities throughout the spine. This was particularly disqualifying. We took a large number of individuals who did have mild scoliosis, but it certainly was much less than 25 degrees.

EXPERIENCE WITH PERIODIC AVIATION MEDICAL EXAMINATIONS

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SUMMARY

This paper will relate personal observations and experience with civilian aviation medical examinations and the Federal Aviation Administration (FAA) certification system from June 1964 through June 1977. Special attention will be devoted to methods used in the assessment of the cardiovascular system. Emphasis is placed upon a systematic approach to those cardiovascular conditions, especially coronary heart disease, which might adversely affect pilot performance, and which present a hazard to public safety. Coronary heart disease and its clinical manifestations are the major cardiovascular problem in United States civilian aviation medicine today. A major objective of assessment is to use evaluation techniques which are useful in detecting potentially dangerous conditions, which are consistent with the highest current standards of the medical practice of cardiovascular diseases, and which are cost effective. From a proper balance of these considerations, a pragmatic methodology has evolved which has met the primary responsibility of the FAA to protect public safety. It has also provided a mechanism which meets a major secondary objective, that is, to keep as many pilots as possible flying safely.

NATIONAL AVIATION SYSTEM

The National Aviation System (NAS) includes all aspects of civilian aviation activity within the United States. This system interfaces with military aviation activities. The civilian aviation activities include commercial air transport, other commercial activities, a large general aviation program, and the elements supporting these activities, air traffic control, airway facilities operations, flight standards operations and procedures, and airport services. The authority to regulate these activities was given to the FAA by Congress in the Federal Aviation Act of 1958. It is the basis for the Federal Aviation Regulations (FAR). Originally the Federal Aviation Agency, this regulatory agency is now part of the United States Department of Transportation. The regulations regarding medical certification of airmen are contained in Part 67 of the (FAR) Sections 13, 15 and 17. The FAA currently employs 65,000 persons whose primary responsibility is public safety, met by administrating the Act of 1958. As of December 31, 1976, there were 780,408 certified active airmen in the United States (1). The medical program is administered by the Federal Air Surgeon and his staff, by 55 full time physician employees, and by 7,638 designated aviation medical examiners. Aviation medical examiners are physicians in the private practice of medicine who have elected to participate in the periodic examination and certification of airmen. They receive official designation by the FAA based upon their qualifications and a need for an examiner in their geographic area of practice. These physicians are highly motivated, usually because of a personal interest in aviation and well qualified, often because of military experience as flight surgeons.

The NAS is divided into ten regions for administrative purposes. Each region has a Regional Director, and working with him, a Regional Flight Surgeon and one or more Assistant Regional Flight Surgeons. The Assistant Regional Flight Surgeons work primarily in the Air Route Traffic Control Centers. They assist in airman certification and are primarily responsible for the medical qualification of air traffic control personnel. They also carry on occupational health programs for FAA employees in their geographic area as required and in accordance with the Federal Health Employees Act of 1948. There were, as of December 31, 1976, 25,677 air traffic controllers who require periodic annual medical examinations. This number has now reached nearly 30,000. There were 15,301 controllers employed by FAA as of that date.

The Civil Aviation Medical Institute (CAMI) is a major resource for the NAS. It has several major functions: research into medical and human factors in civilian aviation and air traffic control; coordination and management of the airman's medical certification system; and, clinical services to airmen and employees. This major resource function is located in Oklahoma City, Oklahoma.

Headquarters staff, supporting the Federal Air Surgeon and Deputy Federal Air Surgeon, include an Aeromedical Standards Division, an Aeromedical Applications Division, a Behavioral Sciences Division, and an Aeromedical Services Division. The Aeromedical Standards Division develops policy regarding airmen certification, proposes regulatory changes, and is the main coordinating point for appeals of denials of certification and petitions for medical exemptions to the FAR. Some examples of this Division's responsibility are investigating the need for the certification of glider pilots, exercise stress testing, etc. The Aeromedical Applications Division develops proposals for specific research investigations. These may be coordinated with CAMI or with outside private sources having special expertise in the area of interest. Some examples of this Division's responsibility are studies in toxicology of combustible materials in aircraft interiors, age 60 airline retirement rule, automated electrocardiogram processing, etc. The Behavioral Sciences Division provides consultation services to the Federal Air Surgeon and develops programs to improve the assessment of NAS personnel. Some examples of this Division's responsibility are dealing with alcohol problems in pilots, air traffic control specialist selection, performance prediction, etc. The Aeromedical Services Division carries out an active program of occupational health, provides general management advice regarding the air traffic controller health program and coordinates medical matters in the area of airway facilities, airports, and flight standards. Some examples of this Division's responsibility are air traffic control specialist consultation services, executive health examinations, general employees health programs, occupational health programs, pre-employment examinations, health maintenance, disease prevention, educational programs, screening, etc. An independent group of non-FAA consultants advise the Federal Air Surgeon on medical matters, particularly those related to the exemption from the regulations of airmen with known medical problems.

AIRMAN MEDICAL CERTIFICATION

Medical certification in the NAS is different depending upon the degree of public responsibility involved. Class I certification is required for airline transport operations. For most other commercial aviation activities, Class II certification is sufficient. The pilot who flies for pleasure requires only Class III airman's medical certification. Air traffic controller qualification standards are contained in FAA Order 3930.3. A Class II airman's certificate is issued with this examination.

In applying for airman medical certification, a standard application form is used, FAA Form 8500-8 (10/73). This form contains applicant identification data, certain demographic data and pilot background information. The latter includes class of certification sought, type of aviation activity, aviation experience, prior certification experience, and general inquiries into past medical experience by body organ systems. Specific cardiovascular inquiries are limited to questions regarding history of heart trouble and history of high or low blood pressure. There is no specific inquiry into socio-economic factors, health and other habits or family history. The findings on physical examination are then recorded by the examiner and the disposition of the case is noted. If the medical history or physical examination indicates any possible problem, no certificate is issued and further documentation is obtained of any questionable item. In addition, special consultations may be required. The guidelines for these administrative matters is contained in the Guide for Aviation Medical Examiners. In the case of cardiovascular disease, requirements for evaluation have been specified (FAA Form 8500-18 (3/77)).

The central repository for all airman medical data is located at CAMI. Initial certification actions on problem cases are taken by the Chief, Aeromedical Certification Branch, CAMI. The authority to review these initial decisions is vested in the Federal Air Surgeon. Except through the exemption process, the Federal Air Surgeon may not apply flexibility (2) or issue a "waiver" in any case in which the FAR requires a mandatory denial certification, such as myocardial infarction. The authority to issue exemptions from the FAR resides in the FAA Administrator and has been delegated to the Federal Air Surgeon where medical standards are concerned. This authority is exercised on the advice of consultant and staff medical specialists. Final denials of certification under the medical standards may be appealed for review to the National Transportation Safety Board (NTSB). The purpose of this review, which involves a formal semi-judicial public hearing before an administrative law judge, is to determine whether the regulations have been properly applied in a given case. Decisions may be further appealed to the full NTSB. If the denial of certification is affirmed by the NTSB, the applicant may ask for review by the Federal Courts and the matter could ultimately be reviewed by the U. S. Supreme Court. It is important to note that each case is considered independently on its own merits, and very little binding law or precedent is set by any one case except in a general way.

CHARACTERISTICS OF AIRMAN POPULATION (3)

The majority of airmen reside in the coastal regions of the United States, the Eastern, Southern, South Western, Western, and Great Lakes Regions. The average age of the airman population is 36.8 years. Almost half (359,005) of all active airmen hold Class III airman's medical certification. There were 79,108 Class I and 298,167 Class II airmen in the active category as of December 31, 1976. The average height for the total population was 70.5 inches for males and 65.0 inches for females. There was no significant difference by class of certification. The average weight for this population was 177.9 pounds for males and 132.1 pounds for females. There was no significant difference by class of certification. In a study by Booze (4), which involved a review of FAA examinations on airmen to evaluate FAA experience with respect to prevalence and incidence of disease by age level, certain specific cardiovascular problems were delineated. The examinations surveyed were a base group certified from 1965 through 1975. New applicants certified in 1965 were also followed through 1975. In this study, the most common cardiovascular condition encountered on entry was hypertension. Heart murmurs were the most common cardiovascular condition for ages less than 30. In the over 30 years age group, hypertension and coronary heart disease were increasingly common, and peaked in prevalence between 55 and 69 years. He found that "prevalence of any type of pathology at entry increases with age from 10% at the younger ages to about 60% at years 75 to 79". He also noted that at re-examination, hypertension was the most frequent condition diagnosed. Myocardial infarction, coronary artery disease, atrial fibrillation, hypertension with heart pathology, hypertension with medication and cerebrovascular accidents all showed a definite increase with age (Tables I, II and III). Table IV indicates the increasing number of active airmen who were certified with hypertension and after myocardial infarction. This general trend has continued, and it is in this group, certified by exemption, that the largest attrition is likely to occur. Of interest is the fact that airmen certified by exemption after infarction, when attrition does occur, even after a 10 to 15 year interval, that attrition is most likely to be due to another cardiovascular event.

AIRMAN EXAMINATIONS

Medical History.

Well performed certification examinations of airmen are no different than any other well performed medical examination. They require knowledge, experience and most of all, time. In aviation, special knowledge of the physiology of flight is also required, and in certification, a working knowledge of applicable regulations is essential. A good examination is usually directed toward an elaboration of medical history, focused on a chief complaint. Within the history, the review of systems is a means of elaborating on the chief complaint, a means of eliciting other symptoms which assist in determining the natural history of a problem from the examinee's point of view and its severity. It is also important in eliciting relevant negative information. Determination of severity usually means the degree of impairment, acuteness or treatability. It may also refer to the point in the natural history, spectrum or continuum of disease at which a given person with a problem finds himself or is thought to be when examined. This last point is critical in most examinations. A person may be, for example, at risk for a disease, such as coronary heart disease. This situation could exist at birth in an individual in whom the family history reveals a frequent incidence of premature death in multiple members before the age of 40 from acute myocardial infarction. Being at risk for a disease is perhaps the earliest clinical concept of disease. It is the

Pathology Codes
By Prefix and Status
As of December 31, 1975
All Airman

TABLE I

Code	Pathology	Disease Status	Issued I	Issued II	Issued III	Issued Subtotal	Denied I	Denied II	Denied III	Denied Subtotal	Pending or Other
483	Hypertension only (labile blood pressure or hypertension without medication)	History of condition	22	399	941	1,362	1	13	38	52	7
		Present condition subject to change	30	367	529	926	42	177	460	679	29
	TOTAL		52	766	1,470	2,288	43	190	498	731	36
484	Hypertension with Heart Pathology	History of condition	2	5	3	10	3	4	5	12	--
		Present condition subject to change	1	7	5	13	15	25	52	92	1
	TOTAL		3	12	8	23	18	29	57	104	1
485	Hypertension with Medication	History of condition	71	515	764	1,350	2	16	47	65	4
		Present condition subject to change	358	1,807	2,340	4,505	64	466	1,357	1,887	128
	TOTAL		429	2,322	3,104	5,855	66	482	1,404	1,952	132

Pathology by Age
As of December 31, 1975
All Airman

TABLE II

Code	Pathology	Disease Status	Less than 25	25-29	30-34	35-39	Over 39	TOTAL
483	Hypertension only (labile blood pressure or hypertension without medication)	History of condition	101	236	181	156	747	1,421
		Present condition subject to change	100	147	131	148	1,108	1,634
	TOTAL		201	383	312	304	1,855	3,055
484	Hypertension with Heart Pathology	History of condition	---	1	2	2	17	22
		Present condition subject to change	1	3	1	4	97	106
	TOTAL		1	4	3	6	114	128
485	Hypertension with Medication	History of condition	21	89	100	115	1,094	1,419
		Present condition subject to change	56	209	327	531	5,397	6,520
	TOTAL		77	298	427	646	6,491	7,939

Pathology by Age
As of December 31, 1975
Air Traffic Controllers

TABLE III

Code	Pathology	Disease Status	Less than 25	25-29	30-34	35-39	Over 39	TOTAL
483	Hypertension only (labile blood pressure or hypertension without medication)	History of condition	2	10	3	3	22	40
		Present condition subject to change	4	15	10	9	66	104
	TOTAL		6	25	13	12	88	144
484	Hypertension with Heart Pathology	History of condition	--	1	1	--	3	5
		Present condition subject to change	--	--	--	--	6	6
	TOTAL		--	1	1	--	9	11
485	Hypertension with Medication	History of condition	1	13	7	19	72	112
		Present condition subject to change	--	12	19	42	312	385
	TOTAL		1	25	26	61	384	497

TABLE IV

ACTIVE AIRMEN

(Certified within the 25 months previous to the date specified)[1]

Medical Condition	December 31, 1970 Class			December 31, 1972 Class			December 31, 1974 Class		
	I	II[2]	III	I	II[2]	III	I	II[2]	III
HYPERTENSION (with treatment)[3]	97	570	1023	158	885	1453	266	1347	1933
MYOCARDIAL INFARCTION (Medical History)	9	119	210	7	145	249	13	136	312

1 Includes both initial issuance and reissue

2 Includes Air Traffic Controllers

3 Control allowed only with Thiazide Drugs

basis upon which much of current medical practice depends, such as, "the annual medical check up", executive health programs, and programs of preventive medicine. Included are screening examinations for diabetes, hypertension, and cancer, and other occupational health activities. All of these programs assume that it is possible to detect risk either from history, physical examination or by some appropriate laboratory investigation. They also require counseling of the examinee, and follow through discussion of significant findings for optimum effectiveness. Much of civilian aviation medicine practiced in the United States today depends upon this conceptualization.

At the present time, this concept is being reviewed by our Aeromedical Standards Division. Reports of recent surveys of aviation accident experiences have alleged that more detailed or more precise examination techniques are needed to reduce the incidence of pilot performance failure in aviation accidents. Recommendations to accomplish this have included having only a single set of criteria for all airmen in order to qualify medically for pilot duties; wider application of resting electrocardiography; incorporation of regular exercise stress testing; a requirement for more extensive blood chemistry screening for latent disease, and changes in the frequency of medical examinations. An optimum system of examination has yet to be agreed upon, and there is still wide variation in opinion among experienced and expert medical authorities on this subject.

Experience with the medical history suggests that most current morbidity and certification denial associated with disease, especially hypertension and coronary heart disease with its complications of angina, myocardial infarction and sudden death, arise from the basic disease process compounded by social and economic factors and poor life long personal habits. At least these latter factors appear to identify the stage upon which disqualifying cardiovascular events are most likely to occur. Numerous long term studies have identified cardiovascular disease risk factors, and these have been used to describe a coronary risk profile. It is for this reason that some authorities recommend a more detailed examination of these factors in every airman medical examination so as to optimize early detection of risk and enable national preventive counseling programs to be put into effect.

Obesity is the most common problem encountered in current civilian aviation medical practice. A statistical evaluation of population data has not shown that obesity is an independent risk factor for coronary heart disease. It is, however, the most prevalent condition in our affluent society. Obesity here is defined as 10 to 15 pounds excess weight over ideal for a given age, sex and height, as compared to actuarial tables. There seems to be good evidence that excess body weight is associated with an increased incidence of vascular disease, including hypertension, coronary heart disease and peripheral venous disease. It is also well documented that obesity is associated with an increased incidence of maturity onset diabetes and other problems, especially musculoskeletal disorders.

Other important risk factors in coronary heart disease relate to habits. Excessive use of tobacco and alcohol occur frequently in airman and air traffic control specialist applicants. These two habits are also often markers for other coronary risk factors such as type "A" personality, high level of perceived stress and resultant chronic anxiety, low threshold for anger and acute anxiety attacks or hyperactivity. They are also associated with poor social adaptation and concommitant problems in interpersonal relationships and economic havoc or complete chaos.

For all these reasons, inquiry should be made of every airman regarding his social and economic background and current status. Also included should be questions regarding his education, attitude towards his work, family and environment, and his general habits regarding tobacco, alcohol, use of drugs, either prescribed or over the counter. Diet and physical activity must also be investigated. The information obtained provides a perspective for the examiner upon which to weigh the relative importance of each factor in predicting subsequent disease experience. It also provides a framework for counseling in an otherwise healthy adult airman applicant with no overt medical problem at the time of examination.

The medical history also provides the data needed to fit any diagnostic "set" for a specific cardiovascular condition. The term "set" is used here to describe a constellation of findings from history, physical examination, and laboratory investigations which allow the physician to diagnose disease risk or disease, to assess its severity or stage, to design or prescribe remedial measures and finally, to estimate prognosis. In aviation, the greatest concern is prognosis for sudden incapacitation. In cardiovascular disease, the history also provides valuable clues for determining functional impairment and provides a basis upon which to estimate the probability of pilot incapacitation in the flight environment. Much additional information is needed to improve predictability in this circumstance. Current prognostication in this area is based primarily upon a thorough knowledge of the disease, its physiologic consequences, and a knowledge of a particular type of flight activity and its physiologic requirements. The ability to match these two aspects of human performance remains unscientific. It requires practicing the art of medicine more than the application of scientific principles even today, with all the advances of the past twenty years. In no area is this more true than in coronary heart disease.

The items of medical history then, which are important in building a diagnostic set for cardiovascular disease are derived from inquiries into the social, developmental, economic and educational history, and from a history of personal habits.

Specific items from the medical history which directly relate to cardiovascular disease are few. Chest pain can be specific. The fact that chest pain of cardiac origin is not pain in the usual sense is more widely appreciated today. It is visceral in type and not somatic. It invariably has a sternal component and is most often described as a heaviness, tightness, pressure or constriction within the thorax. All but 15% of individuals with coronary ischemic pain will describe their symptoms in this way. Precipitation of discomfort by exertion or emotional disturbance is most common. In the latter case, such chest discomfort at rest is not uncommon. Atypical cases of coronary chest discomfort require, for diagnosis, a high index of suspicion by the examining physician. It remains axiomatic that one only finds on history or examination what one asks for or seeks. Unusual equivalents for cardiac pain which have been encountered include exertional coughing, especially at the onset of exercise; supine night cough; awakening from sleep with cough (paroxysmal nocturnal cough), and exertional belching or "indigestion". The physiologic

mechanism for these symptoms is most likely the onset of mild left ventricular failure and a resultant increase in pulmonary venous pressure. This comes about because of an increase in filling pressure of the left ventricle or from a redistribution of blood volume to the central circulation with a marginal functioning left ventricle. The result is some pulmonary capillary transudation and reflex responses resulting in the clinical expressions observed. Other early and subtle expressions of poor myocardial function, often encountered or duplicated by treadmill exercise testing, have been a lack of awareness or alertness, unusual fatigue for the amount of effort performed and observation of marked peripheral vasoconstriction. A gradual reduction in exercise capacity is also frequently elicited by direct questioning as a symptom of poor left ventricular function or poor overall cardio-pulmonary capacity. In chronic diseases of the cardio-pulmonary system, it is natural to adapt ones performance to avoid discomfort and to function within ones capacity.

Palpitations is specific for the heart. This is defined as an awareness of one's heart beat. It is certainly one of the most common cardiovascular complaints and not uncommon in a variety of clinical states not directly associated with any organic cardiovascular disease. Elaboration of the conditions under which palpitations occur is essential for proper evaluation. This includes describing the circumstances under which they occur, possible precipitating or aggravating factors, maneuvers which reduce their occurrance as well as nature of onset, frequency, duration and pattern, regular or irregular. A diuresis has been observed to occur in some subjects after paroxysmal atrial fibrillation or tachycardia. Inquiries on these points alone may permit clinical identification of the problem although further investigation by electrocardiographic techniques is usually required for definite diagnosis and documentation. It is clear that additional investigation is usually warranted in aircrew because of the nature of their duties and also because experience indicates that serious electrical instability of the heart may be variable from time to time in any given case. This variability may include the entire spectrum of cardiac rhythm or conduction disorders in a single airman.

Overt symptoms of cardiovascular dysfunction, such as dyspnea at rest, paroxysmal nocturnal dyspnea, overt pulmonary congestion, right heart dysfunction with venous engorgement, visceral enlargement and edema are distinctly uncommon in the airman population. Exertional "light headedness", overt vertigo or focal or unilateral sensory or motor symptoms, and peripheral claudication are also not common symptoms, even by direct inquiry. Direct inquiry should be made, however, for these symptoms, especially in older airmen, so that early disease of the cerebral or peripheral vascular systems is not missed. These symptoms are important in their own right, but they also may indicate a high probability of coronary heart disease because of the known high prevelance of coronary artery disease with such segmented peripheral arterial disease.

Physical Examination.

Physical examination of the cardiovascular system involves observation of vital signs and an examination by standard, systematic techniques of the heart and lungs and peripheral arterial and venous system. These observations are usually made at rest with the airman sitting or supine. Dynamic observations of the cardiovascular system are today an integral part of cardiovascular examinations. They permit a better assessment of capacity than static observations and also give some insight into the integrity of autonomic control. These observations require little additional time or effort and are easily incorporated into an airman assessment. These observations require the use of multiple positions for examinations, such as sitting, supine, left lateral decubitus, the erect position, sitting leaning forward, standing "spread eagle position" or squatting. Observations are also made with and without respiration, after valsalva, after exercise and after simple isometric exercise. The details of these techniques are available in standard texts, and have also been described elsewhere (2). Most important clinical cardiovascular observations can be made by simple intelligent looking, feeling (palpation) or listening (auscultation).

Each clinical technique is not required in every examination. The application of any technique or all of those available should be determined by the particular problem under investigation and by the medical history, tempered by the experience and judgment of the examiner. For example, the evaluation of the jugular venous pulse is difficult in any case, and its value in the examination of young, healthy subjects is extremely doubtful. On the other hand, it may be diagnostic in some rhythm disorders, such as junctional premature beats, atrial flutter or complete heart block, or in conditions resulting in pressure on volume loading of the right ventricle. In a similar way, the pulse evaluation may be of no special value in routine examinations, except for rate and rhythm. It may, however, give direct information about stroke volume and myocardial contractile state, aortic valvular disease or diseases of the great vessels by the characteristics of its rate of rise or fall or its absence, or by eliciting bruits through auscultation over the cervical, supraclavicular, occipital or femoral areas.

The apex impulse or point of maximum cardiac impulse by observation of its location alone may indicate an increased heart size and by itself, make possible a physiologic diagnosis of cardiac dilatation. This usually coincides with volume loading of the left ventricle. Observation and palpation of the left ventricle (apex) sitting, supine and in the left lateral decubitus positions allows estimation of the contractile state of the left ventricle and ventricular mass (hypertrophy) as well as an evaluation of atrial and rapid ventricular filling. Left ventricular hypokinesis, hyperkinesis or dyskinesis can also be evaluated. Attention to accurate observation and palpation, together with clues from the medical history also indicate what may be found or should be looked for on auscultation.

Examination is completed by evaluation for visceral enlargement, abnormal venous patterns, peripheral pulse examination by both inspection, palpation and auscultation, and examination of the distal extremities for edema or changes in secondary skin characteristics. The latter observations include skin color, temperature, hair changes, and examination of the nails.

The primary purpose of this approach to evaluation is to come to a diagnostic conclusion regarding the physiologic status and functional capacity of the cardiovascular system. Complete assessment usually requires some laboratory observations. It is our practice to obtain, where possible, complete blood counts, especially hemoglobin and hematocrit determinations, urine analysis, a minimum blood chemistry set of

fasting blood sugar, blood urea nitrogen, serum uric acid, and serum cholesterol and triglycerides. A resting electrocardiogram and anteroposterior and left lateral chest x-rays are part of a routine cardiovascular assessment. Data from these tests are then evaluated and the need for more detailed investigation is determined. Any further evaluation is guided by our specifications for cardiovascular examination, and by the particular problem under study. These methods are usually determined by the consultant cardiologist. We expect that the requests for special examinations will conform to current standards of cardiovascular practice and seldom specify any particular investigative technique. For full evaluation, only the above methods may suffice. On the other hand, an accurate assessment of the risk to safety for a given condition in a particular case may require any of the available diagnostic methods in cardiovascular disease. These include vectorcardiography, exercise stress testing, 24 hour monitoring of cardiac electrocardiogram for rate and rhythm, His bundle electrocardiography, echocardiography, radionucleotide cardiology study and cardiac catheterization with angiography. The application of these methods is determined as it would be in any current cardiovascular practice, the exception being that some techniques might not be employed except that the requirements to safeguard public safety and the physiologic requirements of pilot performance in the NAS require it.

Laboratory Studies.

Laboratory studies are not required as a part of any certification examination. These tests are offered as part of the FAA air traffic controller health program, and are taken by 90% of this population. The blood sugar has been most useful in indicating individuals who either are glucose intolerant or have a tendency to glucose intolerance. An overt clinical diabetic state is unusual in our population of airmen by this approach. Cholesterol and triglycerides are used primarily for counseling purposes. The primary approach to abnormalities in this area is weight control. They are also used in coronary heart disease risk assessment and are an indicator for possible stress testing. Abnormalities in uric acid and triglyceride are noted in about 30% of the so-called normal healthy adult population (males) examined. The most common cause of these abnormalities is excessive use or abuse of alcohol. These findings serve as a point of departure for counseling, and also appear to indicate a sub-group of the population who are more prone to a variety of health problems, both psychological and physical. This sub-group also is more apt to become involved in administrative difficulties related to conduct and discipline.

SPECIAL EXAMINATIONS

Ambulatory Electrocardiogram Monitoring.

The ability to monitor the electrocardiogram continuously over a twenty-four hour time interval has added a new dimension to the clinical evaluation of airmen with suspected ischemia. It has also proved most valuable in determining the type and frequency of cardiac rhythm disorders. Data of this type has demonstrated significant rhythm disorders (Figure 1) in general aviation pilots inflight, and permitted proper disposition of problem certification cases. The most common condition seen has been ectopic beats of both supraventricular and ventricular origin. Ventricular tachycardia has been observed in such cases and also in cases of atrial fibrillation as a complicating arrhythmia. This technique deserves wider application in special cardiovascular evaluations of airmen with suspect disease of the coronary circulation. A typical flight for the pilot under evaluation should be included in the monitoring period.

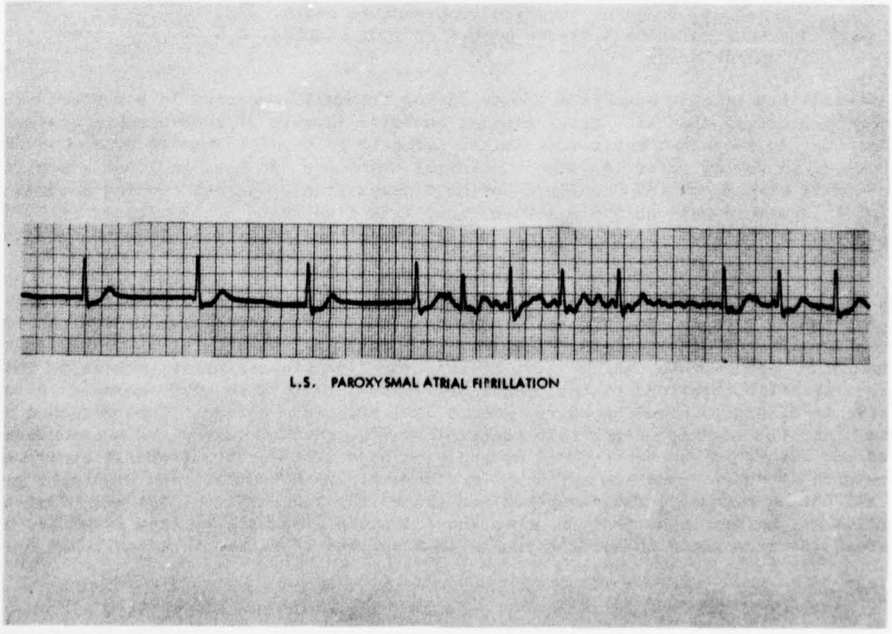


Figure 1. Monitor strip demonstrating junctional rhythm and spontaneous onset of atrial fibrillation after an atrial premature beat. The q-t interval is 0.40 seconds, and the coupling interval is 0.40 seconds.

Exercise Stress Testing.

The current status of the use of exercise stress testing to detect individuals with ischemic heart disease has been discussed by Redwood, et. al. (5). The thrust of this report is that the greatest yield and optimum sensitivity and specificity for this technique is found in populations with a high prevalence of the disease. It appears, therefore, that exercise stress testing is best applied in groups at high risk by other parameters as a step in a total cardiovascular evaluation. This method yields data on functional capacity as compared to a peer group, will detect functional ischemia and significant electrical instability, and does have practical value in aeromedical evaluations. It remains a fact, however, that the only way to specifically identify functionally significant coronary heart disease is by coronary arteriography.

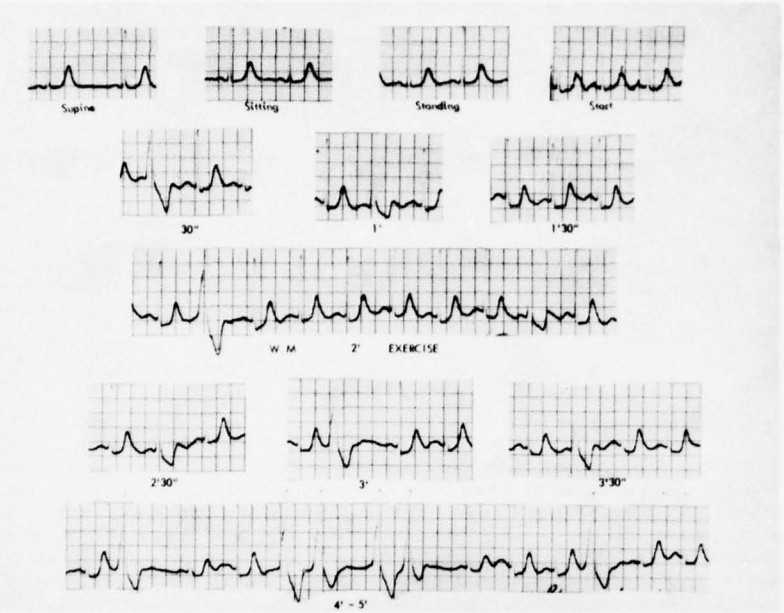


Figure 2. Exercise stress test on a treadmill in a subject with triple vessel coronary artery disease, Ischemic ST changes, frequent ventricular premature beats, and ventricular tachycardia occurs at four minutes, 3.5 mph/4% grade.

Figure 2 demonstrates significant ectopic activity during treadmill exercise in a subject with significant three vessel coronary artery disease. After minimal exercise (Figure 3) some ectopic beats continued into the recovery period. At two minutes after exercise, ischemic ST segment changes were observed (Figure 4). All of these changes in rhythm occurred without clinical symptoms. We have employed a modified Balke protocol in treadmill stress testing developed during a comparison of stress testing methods (6) and (7). This consists of a 15 minute walk at 3.5 miles per hour with five three minute stages of 0, 4, 8, 12, and 16% grade. With this technique, 85% of healthy untrained adult males will achieve age predicted maximum heart rate.

Another useful technique of stress testing involves isometric exercise with a calibrated grip device (Ergometer, Model EM-50, Psytech, St. Michaels, Maryland 21663). The subject exercises at 50% of maximum grip. The usual duration of effort at this level of grip is 2' 30" to 3'. Blood pressure is obtained with EKG prior to exercise, each minute during exercise, and for five minutes after exercise. This stress presents an acute systolic afterload to the heart. Peripheral resistance also increases as shown by the simultaneous rise in diastolic blood pressure. There is little rate change. This response is in marked contrast to the diastolic loading of the left ventricle during rhythmic exercise. Response to a combination of preload and afterload can be assessed by applying hand grip during treadmill exercise. A typical abnormal response to isometric exercise is shown in Figure 5. Both systolic and diastolic pressure increase dramatically, and during recovery, both ischemia and electrical instability (APBs and VPBs) are observed. Isometric exercise may be more sensitive in detecting electrical instability than ischemia, but more data is required before its true place in cardiovascular examinations of airmen is established.

Echocardiography.

The increase in the application of echocardiography in cardiovascular diagnosis during the past seven years has been dramatic. On a practical basis, it is a somewhat tedious technique. In practice, it appears to be most useful in evaluating asymmetrical left ventricular hypertrophy for significant outflow tract obstruction. It is also of value and extensively used in the non-invasive diagnosis of mitral valve dysfunction, especially prolapse of the mitral valve.

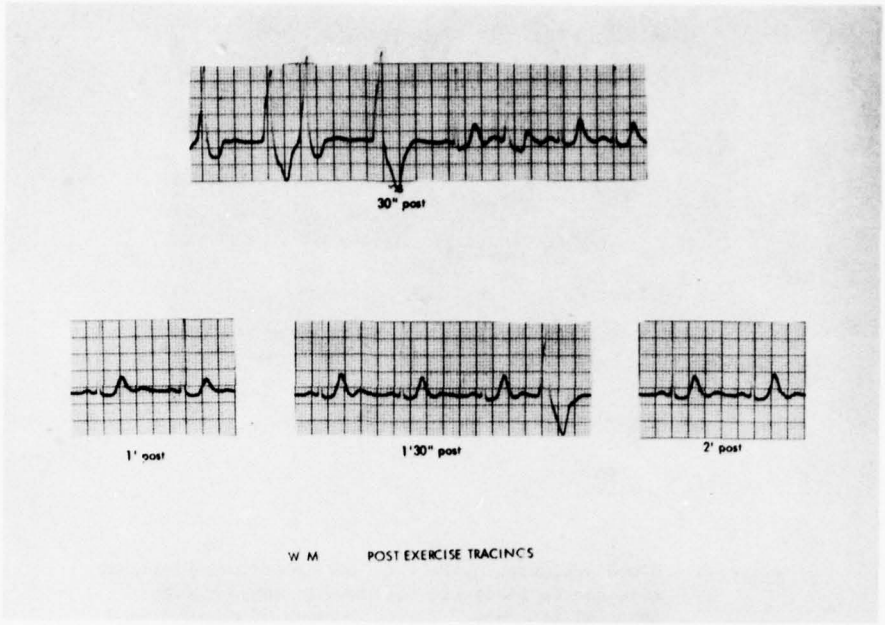


Figure 3. Post-exercise tracings in same subject as in Figure 1.

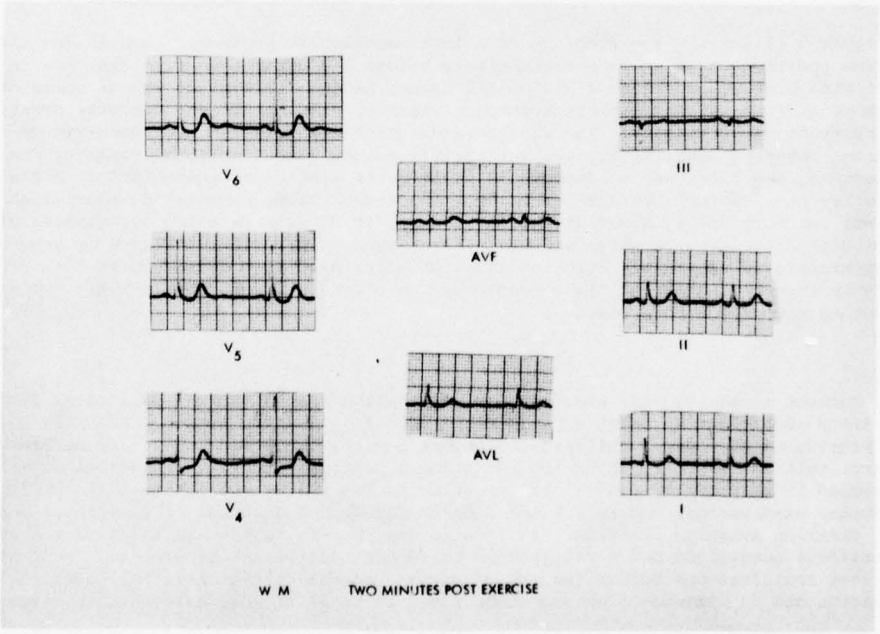


Figure 4. A set of tracings at two minutes of recovery after exercise in same subject as Figures 2 and 3. Electrical instability has cleared. Minimal ischemic ST segment changes persist.

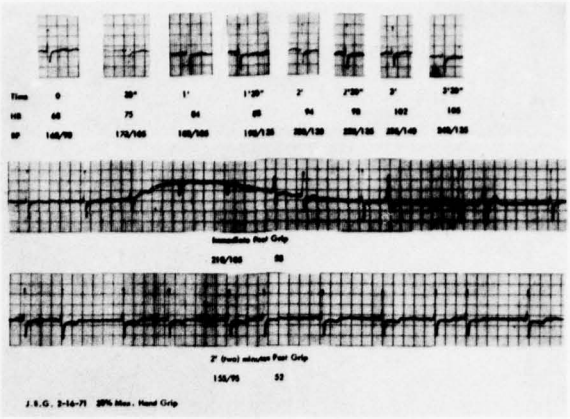


Figure 5. Blood pressure, heart rate and electrocardiographic response to isometric exercise in subject with abnormal response. Thirty percent of maximum hand grip was employed. Both electrical instability and ischemia were observed.

Nuclear Cardiology.

Radionucleotide scanning of the heart has achieved new stature in cardiovascular diagnosis, especially in left ventricular and coronary artery disease. For some applications, it may be an acceptable alternative to cardiac catheterization, coronary angiography, and left ventriculography. This technique has also demonstrated a potential, with or without exercise stress testing, for detecting subjects with functionally significant coronary artery disease (8), and may be useful in the assessment of myocardial function and graft patency after aorto coronary by-pass graft surgery. These applications have been made possible primarily through the use of computers and improved data processing techniques.

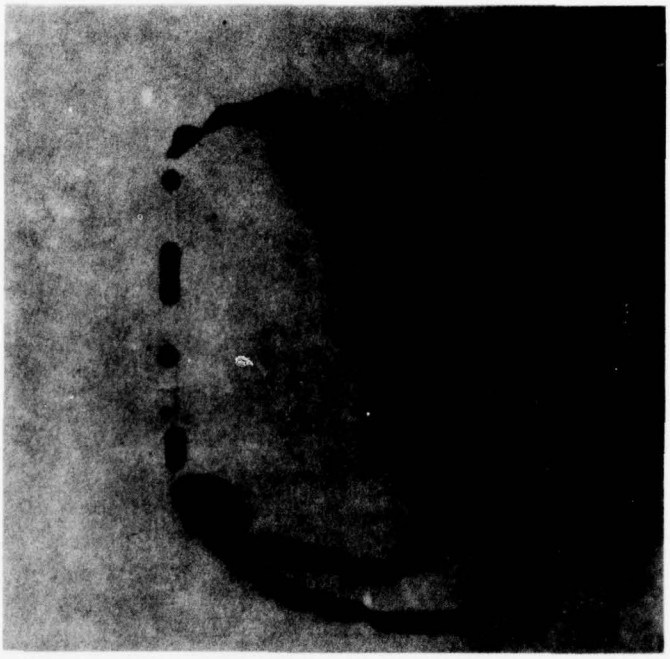
Figure 6 and Figure 7 illustrate the findings on a left ventricular perimeter scan in the right anterior oblique 20 degree position using Tc 99 pyrotechnitate before and after isometric exercise in an airline transport pilot with acquired complete right bundle branch block. This pilot was 42 years of age and was not anxious to undergo cardiac catheterization. Clinical examination and coronary artery disease risk factor assessment were negative. The electrocardiographic change had been observed on serial electrocardiograms required annually for Class I certification. His functional capacity was excellent by treadmill testing, and there was no detectable ischemia or electrical instability. A Thallium 201 scan obtained after near maximal exercise stress testing demonstrated homogeneous myocardial perfusion suggesting normal coronary artery blood flow. The control Tc 99 scan revealed hypokinesia of the left ventricle. Calculated ejection fraction was 58%. After hand grip further evidence of general left ventricular hypokinesis is apparent. Ejection fraction after hand grip decreased to 52%. The conclusion from this study is that this acquired right bundle branch block is due to some primary myocardial disease process, and not to coronary artery disease.

CONCLUSION

In conclusion, current airman medical examinations are minimum investigations of fitness for aircrew duties. The safety record and accident experience of the FAA, however, suggests that the existing certification procedures have empirical value to detect medical conditions which are hazardous to aviation safety. In part, this is due to a continuing educational program for aviation medical examiners. This program is designed to continually update communication of FAA policy, to instruct in the fundamentals of an aviation medical examination, and to provide a forum for direct exchange of experience and ideas for improvement of civilian aviation practice. It is also due in part to the alertness of the examiners to potentially hazardous conditions and a willingness to request additional information, medical documentation and special consultations before issuing an airman medical certificate. Although this process may delay certification and is somewhat slow and cumbersome, it is a valuable safeguard in regulatory medical practice.

Personal experience in regular airman medical certification, in performing cardiovascular consultations in problem cases, in certification of air traffic control specialists, as a consultant to the Federal Air Surgeon, and member of the Administrator's Medical Advisory Panel, indicates that major advances in improving the system might be made with better follow-up on airmen who are denied certification. This information would improve assessment of current practices and policies. Most re-evaluations of policy and practice or proposed changes in rules now come from advances in medical diagnosis and practice, or in medical knowledge. Some changes are brought about by new therapeutic techniques as in the case of aorto coronary by-pass grafting procedures.

PL, BKGD, DT CRCTD		PAT DP	STUDY NUM	2768
ORIENTATION	90		FM N-MAX	200
ACT LEVEL	45		ACT RANGE	49
TOT CNT	29300			
AUG			ACCU TIME	1.00



CONTROL

Figure 6. Control Tc 99 perimeter scan of the left ventricle in RAO 20° position. Ejection fraction 58%.

PL, BKGD, DT CRCTD	PAT DP	STUDY NUM	2768
ORIENTATION 90		FM N-MAX	200
ACT LEVEL 45		ACT RANGE	49
TOT CNT 25900			
AUG		ACCU TIME	1.20

AFTER HANDGRIP

Figure 7. Repeat Tc 99 perimeter scan in same subject after 50% maximum hand grip. Ejection fraction 52%.

Finally, more detailed medical knowledge of individual airmen, more intensive examinations, and a policy of close medical surveillance allows more pilots with known problems to maintain flight privileges at no risk to public safety. Personal experience indicates that an aviation medical examiner is most effective when dealing from personal knowledge on an individual basis with members of a cohort of aircrew.

This optimum situation is difficult to achieve. It is approached by FAA physicians in Air Route Traffic Control Centers, and is possible for individual aviation medical examiners in their own geographical area. It is inefficient, however, and remains costly in terms of time and money. There is a continuing need for experienced personnel as well.

All in all, the current certification system appears to be a satisfactory, practical compromise between the ideal medical evaluation and the existing constraints imposed by the scope and size of the United States National Aviation System.

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DISCUSSION

Leguay: I wish to ask you a question on the continuous recording of the 24-hour ECG. How frequently do you do it, what are the results, and what are the conclusions related to aviation medicine, when extra systoles are present? And, finally, what are your recommendations?

Westura: We are requesting them increasingly. It is not a routine procedure so far as our cardiovascular specifications are concerned. But when we do find someone who has an arrhythmia, even if it is only periodic ventricular premature contractions, I think it is important to get some dynamic idea of what is happening over a 24 hour period. Now, if they show runs of ventricular tachycardia, we would not recommend return to flying duties. If the premature ventricular beats have a long coupling interval (that is an RR - QT ratio greater than 0.89), we would probably allow that individual to fly with surveillance.

Triebwasser: Do you return pilots to flying duties who have experienced an episode of atrial fibrillation? The first case you presented appeared to be in atrial fibrillation.

Westura: We do not allow airmen to fly with chronic atrial fibrillation. We usually require that they be in a normal sinus rhythm for a six month period on no medications before we will certify them. With rapid ventricular response, as seen in the first case I presented, I think he is a hazard to himself and to others. Therefore we turned him down.

Fitzgibbon: I would like to make a couple of comments on simple things and then more complicated ones. The simple things first of all. I couldn't agree with you more that it is very important to have some fingers and to listen very carefully for 4th heart sounds. But, how do you manage to teach your medical examiners in the field to do this? It is all very well for you to do this in Washington. But when somebody talked earlier this morning, about a thorough physical examination, their physical examinations are not really very good in coronary artery disease detection unless they are done by good physicians who know what to listen for and what to feel. So what educational program do you actually have for these medical examiners who are scattered all over the United States?

Westura: We have a continual educational program which comprises about two seminars per month. I participate in about half of them and what we try to do in those sessions, is to emphasize physiology including the pathologic physiology if you will, of those sounds. Now, an atrial sound can be normal, but if it is accompanied by a palpable presystolic thrust at the apex, that's abnormal. It is a subtle differentiation but still nonetheless it is a matter of continual education for the AME's. I can recall calling a colleague during my training and saying this man has angina and an atrial sound, and the colleague saying back to me, "Well doesn't every one". It's a matter of educating yourself to listen carefully and placing them in the context in which you have found them.

Fitzgibbon: Yes, I agree entirely. There is a current argument about the significance of the fourth heart sound. I think Spodic is one individual who is most concerned with defining the significane of these sounds. I'm talking about the average young pilot, the 30-year-old, who normally does not have a fourth heart sound. But if he has coronary artery disease, you can easily precipitate this by having him sit up and touch his toes ten times. This is a very useful and simple little test. Do you do this with your hand grip tests, that is listen for a fourth heart sound before and after isometrics?

Westura: I spent a year in the Air Traffic Control Center examining young controllers for the most part, and my experience is that atrial sounds or fourth heart sounds are very uncommon. I don't recall in the whole year's work there that in the group between 26 and 50 years of age, finding significant atrial sounds unless there was present hypertension, coronary disease, or something else. And it is very remarkable to me that clinicians always state the heart rate should be between 60 and 100. Well, in the normal air traffic controller population it is around 48 or 52. You just don't hear atrial gallops in these people, nor do you feel them.

Fitzgibbon: My other question has to do with the hand grip test. I wanted to specifically ask if you do listen for heart sounds before and after isometric studies?

Westura: I always do a complete physical examination before I do any stress testing. Then after a hand grip test, I always listen carefully for fourth heart sounds. It is crucial to listen not only at rest to get a good control, but after exercise, whether it be hand grip or treadmill.

Fitzgibbon: My last question has to do with the patient's addition/subtraction scintigram you illustrated. His radionuclide studies appeared to be very valuable. You ended up your synopsis of his history by saying that he had normal coronary arteries. This, of course, was a surmize because he had refused coronary angiography. He had a hypokinetic left ventricle and he presented initially with right bundle branch block. Would you not think that right bundle branch block and a hypokinetic left ventricle to that degree, add up to a cardiomyopathy? I would be disinclined to fly across the Atlantic behind that fellow.

Westura: Yes, I agree with you. The main criteria for returning him to flying duties based on recommendations from consultants who are much more expert in the technique than I, that is, the ejection fraction. This man's ejection fraction was 58% at rest and 52% after exercise, both being above 50%. On basis of these normal ejection fractions and normal treadmill tests, we elected to certify him for flying.

Joy: I would like to ask what your attitude is to the problem of parasystole? We have certainly diagnosed parasystole a couple of times in the last year. One of these individuals experienced ventricular tachycardia on treadmill testing. The others are under investigation at the present time. Since it is often recommended they be relicensed, I just wondered what your attitude to that was?

Westura: I surveyed a group of cardiologists in the U.S. and among those, was Dr. Anthony Damato who is an expert, if you will, in His bundle recordings and in electrocardiography. The consensus was that parasystole is a benign phenomena. I have not seen ventricular tachycardia after exercise as you have. In general we would not disqualify someone on the basis of parasystole.

Joy: What is the frequency of it in your experience?

Westura: It's about 12 cases per year, very small.

Triebwasser: We see parasystole very commonly in our flying population during 24 Holter recordings. Our policy has been to let these people fly providing there is no other indication for malignant VPB's such as couplets, multiformed beats, etc.

A PROSPECTIVE MEDICINE APPROACH TO THE PROBLEM OF ISCHEMIC VASCULAR DISEASE IN THE USAF

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SUMMARY

A program of ischemic vascular disease (IVD) risk factor identification and intervention is being developed for demonstration in the U.S. Air Force. This program should form a model of prospective medicine and the basis for revision of the periodic physical exam ination. If successful, the IVD model would form the foundation to which other health predictions could be added as sufficient information became available.

I. BACKGROUND

Of all the health problems facing the developed countries of the world today, cardiovascular disease, particularly coronary artery disease and the consequences of high blood pressure, is the single most important from the personal and economic viewpoint. In the United States, more people die of cardiovascular disease than all other causes combined. Further, a large proportion suffer crippling illness and death during their most productive years. The Air Force shares this problem since cardiovascular disease also affects the individual airman, officers, and the Air Force in the same way. In considering the financial impact alone, cardiovascular disease currently costs the Air Force over $100 million yearly.

The problem of ischemic vascular disease is compounded when it is realized that the disease begins early in life, either in infancy or childhood, and progresses to present as a sudden catastrophic event in one out of five American males before the age of 60 (1). Over 65% of American males developing ischemic vascular disease before the age of 60 will have their first symptom be a myocardial infarction, and over 25% of the patients will have sudden death as their first clinical manifestation. By the time individuals develop symptoms of cardiovascular disease, three-fourths of the population will have 90% or more obstruction of one coronary artery and over half will have a total occlusion of one or more vessels (2). It is evident, therefore, that there are more relatively young people with coronary disease who are asymptomatic than there are symptomatic patients.

The routine periodical physical examination, although logically a valuable tool for the early detection of disease, has come under increasing question in the past few years. Several studies have recently been conducted to assess the value of the routine examinations, and these studies raise serious questions about the effectiveness of this approach. This is particularly true with reference to the early diagnosis of ischemic vascular disease. The current scope of the routine periodic physical examination will detect the symptomatic patients, the patient with significantly elevated blood pressures, and the patient with an abnormal resting electrocardiogram. Clearly, symptoms will not be uncovered in the majority of patients because most are asymptomatic. In addition, there are problems concerning the administrative disposition of individuals with an elevated blood pressure, and in practice, it is common to find that hypertension has been ignored. Additionally, since the relationship of the risk for cardiovascular disease is directly correlated to the level of the blood pressure in a linear fashion, the patient may be at increased risk although his blood pressures are within the range of acceptable levels for administrative purposes. Although the routine resting electrocardiogram is a valuable tool in the screening of an apparently healthy population for heart disease, it is well recognized that it is far less sensitive than the ideal and in addition, many of the findings are nonspecific even when the electrocardiogram is abnormal. From 15 to 30% of patients experiencing a classical myocardial infarction will lose the diagnostic features of the electrocardiogram, often within months after the event and thus, the periodic electrocardiogram may miss a myocardial infarction (3). Additionally, it is well known that individuals with significant coronary heart disease, to the extent that they suffer frequent bouts of angina pectoris, may have completely normal electrocardiograms even if the tests are made periodically and carefully compared serially. Although not a part of the routine periodic physical examination in the Air Force, maximal exercise treadmill stress testing can significantly improve the detection rate of asymptomatic ischemic vascular disease. Abnormal treadmill tests have shown a risk ratio of 14:1 over negative treadmill tests for the subsequent development of clinically evident ischemic vascular disease in a six-year follow-up period. However, the predictive value of an abnormal treadmill test was only 20%, and the sensitivity only 61% (4). Therefore, the addition of maximal treadmill exercise stress testing as a routine screening procedure to the periodic physical examination would significantly improve the detection rate of asymptomatic ischemic vascular disease, but the resources required to apply this test to the entire Air Force population are not available. A large part of the criticism of the routine periodic physical examination has come from the lack of cost effectiveness in such examinations.

Over the past several years, worldwide studies have shown that individual susceptibility to many cardiovascular diseases can be predicted reliably using risk factors as indicators. Furthermore, interventions directed at specific risk factors in individuals who are at high risk can delay or prevent many of their serious consequences. By collecting the more important risk factors, utilizing them, and determining a combined risk for the individual, and then concentrating efforts on those at high risk, it is likely that the cost effectiveness of the periodic physical examination could be significantly improved.

Because of the above consideration, a proposal was submitted in May 72 that the Air Force consider developing a program of coronary disease risk factor identification and risk reduction. The proposal was

reviewed and strongly indorsed in a final report in Apr 74 by the Air Force Scientific Advisory Board in counsel with a number of internationally known medical figures. The Air Force has now begun the development of such a program.

II. THE PROPOSAL

A. Risk Identification

1. Periodicity

Patients would generally enter the program via the routine periodic physical exam. The periodicity of the examination would be modified by optimizing with respect to resources available using mathematical modeling of the Air Force population. The current periodicity of the physical examination, as directed by AFR 160-43, would be modified to insure inclusion of the younger individual in the Air Force population into the risk screening program in a more timely fashion than would be true currently. For example, officers and airmen not on flying status are not required to have periodic medical examinations until age 27 and thus may spend eight years or more in the Air Force without benefit of risk identification.

2. Scope

The initial screening evaluation for this plan would include those items currently required by AFR 160-43 with the exception that the portion of the physical examination currently conducted by physicians would be deleted. Additional data would be collected, which would include serum cholesterol, serum triglycerides, fasting blood sugar, and risk factor data on a special questionnaire designed for use in combined risk calculation. Risk factor data to be collected would include age, sex, cigarette smoking history, alcohol consumption, exercise habits, individual history of cardiovascular disease, family history of cardiovascular disease, height, weight, systolic and diastolic blood pressure, electrocardiogram, serum cholesterol, serum triglycerides, and fasting blood sugar. Additional research will be required before final determination of the complete risk factor set to be used. Evaluation must be pursued in regard to practical methodology for assessing stress, such as the life changes Index (Holmes and Rahe) and Jenkins activity survey. The desirability and practicability of separating cholesterol in alpha and beta lipoprotein fractions deserves further study. The exact role of exercise stress testing and its application in the risk evaluation will have to be determined.

3. Risk Calculation

Current work is addressing the question of the best statistical approach to individual risk calculation, as well as the best methodology for handling the population data. An individual risk calculation will be performed which will identify the current risk for the individual and will also project the effect of modification of individual risk factors upon the combined risk figure. The combined risk figure will be a threshold for determining the disposition of the individual with reference to the risk reduction program.

B. Risk Modification

1. General

The entry criterion for an individual into a risk modification program would be the combined risk assessment. The utilization of the combined risk assessment associated with the periodic examination would offer many significant advantages over our present approach. Obviously, the most significant advantage would be the opportunity to intervene and to prevent at least some of the personal tragedy of premature death and/or disability associated with ischemic vascular disease. Although the data supporting the concept that ischemic vascular disease is preventable is not complete, that conclusion is inescapable. Cigarette smoking constitutes an avoidable risk and cessation of cigarette smoking is followed by reduction in ischemic vascular disease risk, especially in the younger group (5,6). The ex-smoker approaches the nonsmoker risk of death from ischemic vascular disease after 10 years of abstinence from smoking, but the risk of lung cancer drops more rapidly. For patients with diastolic blood pressure elevations in the range of 90 to 114 mmHg, drug treatment has produced a decrease in the risk of developing a morbid event over a five-year period from 55% down to 18% (7). While the treatment was most effective in the prevention of congestive heart failure and stroke, and least effective in preventing coronary heart disease, the data currently available support the judgment that effective, long-term therapy for hypertension may help prevent coronary heart disease as well as other ischemic vascular disease. There is no conclusive data that would allow one to determine the effect of lowering serum cholesterol on the risk of developing ischemic vascular disease. However, there is substantial indirect data that would infer that faith in the efficacy of lowering serum cholesterol is justified. Dietary studies in both animals and man are available to support this hypothesis.

Intervention into each of the above example risk factors requires a modification in life style of sufficient extent and in enough individuals to significantly impact the problem of ischemic vascular disease. Success rates for one year continued cessation or marked reduction in cigarette smoking have been in the range of 20 to 30% (8). Control of hypertension in large out-patient populations has been achieved in 90% of the treated patients with a compliance rate in the range of 90%. Lowering of serum lipids can be achieved in the majority of patients by dietary change, exercise, weight loss, and/or drug therapy. Approximately 60% of the subjects in the United Airlines study had a decrease in lipids during the first year of clofibrate therapy and an additional 20% over the second and third years (9). Thus, it appears completely reasonable to predict that sufficient alteration in the major risk factors could be achieved in a large population to have an impact.

A mathematical model constructed for the Air Force population predicts within 10% of the actual Air Force case rate for ischemic vascular disease. Using this model, the effect of changes in risk factors achieved through intervention therapy can be projected. We used a five-year linear washout period for full effect of a favorable change in risk factor level. The results of a series of changes in risk level are demonstrated in Table I. Using the levels of change that can reasonably be expected to be achieved, the model predicts a decrease in case rate of 18%.

In addition, other positive effects could be expected from this approach. Identification of individuals at increased risk would allow medical intervention at the earliest possible phase of the disease process. There would be a specific feedback to the patient from the routine periodic physical examination and specific findings would be more likely to motivate compliance than do generalities. There is the opportunity to optimize the delivery of health care, i.e., extending scarce medical resources on the relatively small subset of the population from whom the majority of ischemic vascular disease would come. A program of risk assessment and risk intervention would serve as a model for expansion of prospective medicine principles to a broader base, such as the physical exam program and re-evaluation of medical standards for flying.

2. Methods

a. Personnel

It is considered that the most logical individual to be the base level program manager would be a nurse (probably an environmental health nurse) supported by medical technicians currently involved in periodic physical examinations. Additionally, the primary risk modification program would be supported by ancillary personnel, such as community volunteers and social actions personnel. Personnel from the primary care medical facility would retain their traditional roles as consultants to the program manager without having primary responsibility in the risk reduction program. These personnel would include physicians, dieticians, social workers, psychologists, etc.

b. Behavior Modification

It is considered that the group approach to risk factor modification through behavior modification would not only be more practical than a one-on-one type of approach, but also would be more effective. This has been validated in the experience of numerous groups, including Alcoholics Anonymous, TOPS, Synonon, and others. It is envisioned that individuals would be referred into the Risk Modification Program and follow-up appointments made by the program management, but the individual group endeavors would be carried out by ancillary personnel. A good example is the current Stop Smoking program of the American Cancer Society, which is achieving noteworthy results in several voluntary programs. These programs call on community volunteers for the maintenance of the program. Also, there has been considerable success with self-monitoring or self-control techniques in the management of obesity, type A personality, and drinking behavior. It is considered that social actions officers would be ideal contributors to this program since each one has had behavior modification training.

c. Education

A major portion of the program hinges upon an excellent education method. The educational materials will include those required for general population education to call attention to the program and to convey general information to a broad population. This portion of the program also includes the development of sophisticated briefing materials for use by the program manager to reach the population in personal presentations. Another aspect of the education program involves the requirement to enlist the complete cooperation and backing of the USAF medical corps for the concepts of this program. The other aspect of the educational program involves those materials needed for individual patient education. It is obvious that individuals entered into the Risk Modification Program will need specific information with respect to what needs to be changed, why it needs to be changed, and how to change it. This, for example, would include an effective education program on the relationship of serum lipids to heart disease risk, the role of diet, exercise, obesity, etc., in the control of lipids, and specific instruction in modification of the individual's dietary life style. It is considered that these educational materials should be developed using the most advanced approach, which includes determining the objective, development of the education materials, and determining the effectiveness of the product. It is evident that this is an extensive development effort and that materials should be standardized for use throughout the program. These materials would be applicable for the medical facilities to use in patient education programs throughout the Air Force.

C. Program Planning and Management

1. Operations Research Model

It is considered that the most effective way to plan and modify the program based upon experience would be to base the plan upon a sophisticated operations research model. When completed, this model would allow planners to determine the impact of using various risk levels as decision factors in determining whether or not an individual goes into a risk reduction program. By utilizing the modeling approach, it should be possible to optimize decisions in the plan with respect to various criteria, including cost effectiveness, as opposed to making an a priori decision on individual factors. Although the modeling effort will require certain assumptions about data that is not currently available, there will be the opportunity to improve these assumptions with experience and to modify the impact on the program through the output of the model.

2. Information System

It is evident that in order for the base level program manager to effectively utilize the medical risk data acquired, he must have available a usable and effective information system. It is also required that this information system provide data into the central operations research model in order that the program may be monitored throughout its duration. This information system has not yet been specified. It may vary from a set of forms on to an interactive computer communications terminal. Regardless of the exact form, this part of the program is the key segment as far as user acceptance is concerned.

3. Personnel Training

A core curriculum must be developed, including the cost and resources required, for training the key individuals as base level program managers. It is considered that this can most effectively be accomplished in a central location. This core curriculum must have available the needed educational materials, the training syllabus on behavior modification and completed information system prior to beginning training.

4. Plan

An Advanced Development Program Office has been established at the USAF School of Aerospace Medicine to manage the development of this program, which will be primarily done on contract. The program office will also monitor the test phase of contract.

5. Test Program

It is considered imperative that a trial program be implemented for one year at at least three Air Force bases. These bases should be selected on the basis of criteria that will maximize the approximation to the Air Force in general; therefore, it is considered that an operational base of moderate size with a small medical facility, a medium size operational base with an intermediate size medical facility, and a large operational base with a large medical facility should be selected if possible. It would also be desirable to have one of these bases located in a relatively isolated geographic location. The purpose of this test phase would be to identify and work out the logistical problems in doing such a program and not to demonstrate or test the validity of the concept involved. This test phase would allow validation or modification of the assumptions made in the operations research model and would provide the keystone data for determination of whether or not to implement the program on an Air Force-wide basis.

TABLE I. MODEL PREDICTIONS FOR VARIOUS THERAPEUTIC INTERVENTIONS

RISK FACTOR REDUCTION	DECREASE CASE RATE
SINGLE RISK FACTORS	
↓ SBP ≥ 140 in 60%	5.0%
↓ SBP ≥ 140 in 80%	6.7%
↓ CHOL ≥ 220 in 10%	2.7%
↓ CHOL ≥ 220 in 20%	5.4%
↓ SMOKERS by 10%	2.4%
↓ SMOKERS by 20%	4.8%
↓ SMOKERS by 30%	7.2%
COMBINED RISK FACTORS	
↓ SBP ≥ 140 in 80% ↓ CHOL ≥ 220 in 10% ↓ SMOKERS by 10%	12.5%
↓ SBP ≥ 140 in 80% ↓ CHOL ≥ 220 in 20% ↓ SMOKERS by 20%	16.0%
↓ SBP ≥ 140 in 80% ↓ CHOL ≥ 220 in 20% ↓ SMOKERS by 30%	18.6%

Abbreviations: SBP = systolic blood pressure; CHOL = cholesterol. Model assumes Air Force population has same distribution of risk factors as Framingham population. Percentage reductions in risk factors indicate that at and above the threshold value, each risk level was reduced by the stated percent and those individuals affected were proportionately redistributed in the population below threshold value.

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DISCUSSION

Clement: You had a very impressive and useful program. I wonder however, if it is feasible. Let's suppose your model which necessarily must rely on operational analysis of the data, can provide an equation which is capable of estimating the risk of a cardiovascular accident in the future. And, let's suppose this model is exact. I'm not sure that even when one has such a model, one would be able to change the risk factor afterwards. Let's take an example. Suppose the model states those who have 50 mg% more cholesterol than another would have 30% more risk of a cardiovascular accident within the next 10 years. This does not necessarily mean that if you reduce the cholesterol by 50 mg%, you would effectively reduce the risk by 30%. The model should also rely on longitudinal data. Now that takes 20 years. Do you think you should start with such a huge program?

Lancaster: Do we have enough evidence today to say for sure that modification of risk or individual risk factors, will result in a decrease in mortality and morbidity rate from coronary disease? The answer to that is no, we do not have sufficient evidence to be certain of that. There are some hard data that I think is sufficient to allow us to make a decision. Now we can wait 20 years until someone really demonstrates that a decrease occurs and then we can set up a program, or we can take the data available today, and make as intelligent a decision as we are able and go ahead and implement a program. I think the data about cigarette smoking is hard enough to make a good clear decision on. Individuals who have been cigarette smokers and stopped, revert back to a nonsmoker mortality within 10 years. I think the data on hypertension is encouraging. I frankly think that the trials that have been done, like the VA cooperative study in the United States, have been a bit misleading in that they waited until there was well established disease before attempting to see if modification of risk factors will influence mortality and morbidity. Nevertheless, the data is still encouraging. Now, let's say just for the moment, there is essentially no data that says reduction of cholesterol will result in a reduction of mortality and morbidity. At the very least that is controversial. But, I think we all feel that modification of cholesterol will in fact result in a decrease in the actual event rate sometime down stream. It seems to me that if you start at a very young age with intervention in cholesterol, you are much more likely to reduce the true risk than if you wait until the man is 45 and he has had a high cholesterol for 25 or 30 years. Now, if you take these three risk factors and plug them into the model, using a five year linear wash out curve so that you do not have instantaneous change in event rate, you will find that within completely reasonable rates of change of risk factors (in other words, reductions of risk factors that have been accomplished by others), you will get a net cost savings from the program. So, my answer is I believe it's worthwhile implementing this now. We are not implementing this across the whole Air Force to begin with. If we were to find that we could not do this in the Air Force setting, or if we were to find that doing what we are doing does not result in significant risk factor reduction, then we have a point where we can decide not to implement it across the whole Air Force.

Money: Several speakers today including yourself, mentioned with a noticeable lack of enthusiasm, that physical exercise is a factor in reducing cardiac risk. I wonder if you could say something about the nature of the evidence for that.

Lancaster: I would modify your statement about what has been said. I think most of what has been said is that there is no good solid evidence that sedentary activity is in fact a significant risk factor, and the opposite of that is exercise could not be expected to reduce risk significantly. My own personal feeling is that exercise is an excellent adjunct to total physical conditioning. However, I believe there are far more important things in which we could invest our time, like getting people to stop smoking cigarettes, controlling their hypertension and modifying their diet, rather than to worrying about their exercise. I do believe it's a good adjunct to weight control and perhaps in helping alleviate stress. I'm enthusiastic about it as a general recommendation; but, it's really way down in my list of priorities as an intervention technique.

THE SIGNIFICANCE OF RHYTHM DISTURBANCES IN ASYMPTOMATIC PERSONS

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SUMMARY: Nearly all rhythm disturbances can be found in persons without clinically significant heart disease. New ECG methods and epidemiologic studies help to clarify their prognosis. The results of such investigations are of special importance to aviation medicine, because arrhythmias can cause sudden incapacitation. This paper only deals with those arrhythmias occurring in a well controlled asymptomatic population such as flying personnel. It bases on the literature as well as on the results of long-term ECG recordings on pilots and outpatients. The immediate hemodynamic consequences of these ECG alterations and possible prognostic implications for the incidence of sudden dangerous arrhythmias shall be discussed.

The observation of younger and middle-aged persons in normal physical condition without heart disease by means of new ECG registration methods has shown an astonishing number and variety of rhythm disturbances. Nearly all clinical recognizable arrhythmias are reported (16). In this connection the question is of great significance wether such ECG anomalies have to be classified in some instances as premonitoring phenomena of subsequent heart disease.

In flying fitness examinations the arrhythmias are the most frequent ECG findings except for the ST-alterations. Because of the specific stress situations of the pilot judgement of rhythm disturbances has to be considered from a different point of view than in the average population. A special question is posed when such dysrhythmias can exacerbate to dangerous ones respectively if hemodynamic sequelae have to be feared especially in extreme flight situations. In this respect it will be interesting to delineate possible alterations of hemodynamics and criteria that may indicate an acute worsening of these ECG findings under abnormal conditions or a later coming heart disease.

Based on findings and evaluations in the literature results of ambulant 8-hour ECG recordings on 108 asymptomatic members of the flying personnel of the GAF and of ambulant 24-hour ECG recordings on 550 outpatients of the Medical Policlinic of the University of Wurzburg with semi-automatic and computer based analysis are discussed.

Incidence of dysrhythmias in seemingly healthy people: Dysrhythmias in the routine ECG in larger non-selected groups are relatively rare, the reports differ between 2,5 and 8 % (1, 8, 14). In long-term ECG observations, however, up to 92,3 % of all examined had such findings at a given time (6, 19, 26).

Premature beats: This is especially applicable in case of extrasystoly, far the most common arrhythmia. We found it in 2,5 % of the routine ECGs of the flying personnel of the GAF (13). AVERILL reported 1,1 % in the USAF (1), BLACKBURN 5 % of a male group (3). In long-term ECG studies the percentages are much higher, namely 31 - 76 % in regard to supraventricular premature contractions (SVPCs), 29 - 62,2 % ventricular premature contractions (VPCs), even 8 - 33,2 % multifocal VPCs (14, 19, 26).
Clinically healthy persons seem to show premature beats in the same frequency like those with cardiovascular diseases (22). All foci may also occur within the hearts of asymptomatic people (16). Even the existence of two or more foci is of less importance than their common activity (14). We found a coexistence of SVPCs and VPCs in pilots (16,3 %), also singular multifocal VPCs (10 %), even though restricted to long-term ECG observations (13). A comparison of the distribution of the different types between pilots and outpatients show that the unifocal VPCs prevail in healthy people, the multifocal in patients like the SVPCs and the combination of SVPCs and VPCs in this group with a higher average age. Their pure existence is therefore less important than their noted frequency.

a.) SVPCs: The SVPCs have no reported influence on life-expectancy (21). Because of their more frequent existence in advanced age they have been attributed to the senile myocardial degeneration. Also in younger people their high occurrence and especially a short coupling interval show the possible release of supraventricular tachycardias. Nearly all of these arrhythmias (84 % of all supraventricular paroxysmal tachycardias, 81 % of all paroxysmal atrial fibrillation) in our patients were triggered by SVPCs with short coupling. Therefore the criteria which require a more accurate diagnostic work-up in asymptomatic persons with SVPCs are a frequent occurrence and a short coupling.

b.) VPCs: The same applies to VPCs. Because of their coincidence with higher-grade ventricular dysrhythmias more attention is paid to them. The results of epidemiologic studies, of long-term ECG observations, particularly in intensive care units show the importance of the following criteria:

1.) Frequency of occurrence
2.) Multifocal origin
3.) Pairs or runs
4.) R-on-T phenomenon

Some studies demonstrate the relationship between these signs and sudden death on coronary heart disease (CHD) (4, 7). We have observed a R-on-T phenomenon also in healthy persons without release or coexistence of ventricular tachycardias. We believe that such a mechanism doesn't play an adverse role in an unaltered myocardium. Nevertheless a prediction is not possible how such shortly coupled premature beats behave under extreme circumstances in flight-situations, e. g. hypoxia, hyperventilation, intrathoracic high pressure, g-acceleration.
Theoretically the PVC then could fall into the vulnerable phase of the antecendent normal beat because of Q-T lengthening and thus release a dangerous ventricular arrhythmia. Exercise-dependent increasing PVCs are likewise not rare in healthy persons and usually without consequences (14, 20, 21). In CHD-patients with this kind of arrhythmia, however, a higher mortality is described (23).
In randomized studies VPCs per se indicate a higher mortality than SVPCs or absence of premature contractions. The possible reason is the inclusion of coronary patients in these groups. RODSTEIN describes significantly that there is no increased mortality with subjects who have PVCs without heart disease. On the other hand he found a markedly higher mortality in people with demonstrable cardiovascular illness (21). The normal, at least not ischemic myocardium is probably less vulnerable to re-entry mechanisms and focal irritability.
Also the hemodynamic consequences of premature beats are neglegible in healthy individuals, particularly in absence of coronary and cerebral sclerosis. CORDAY figures in his animal experiments that the reduction of internal carotid blood flow in frequent SVPCs amounts to 7 %, in frequent VPCs to 12 %. The coronary blood flow was dimmished by 5 % in SVPCs, by 12 % in VPCs (9, 10).

The necessity for cautious individual approach should be emphasized in respect to frequent, short coupled PVCs, when dealing with healthy pilots. The reason is the hypothetical, yet unproven danger of triggering arrhythmias of higher grade. In these cases and in individuals with subjective complaints the use of beta-blocking agents could be considered even in a flying population. We found a 50 %-reduction of these arrhythmias under application of these drugs without essential side effects (15).

Tachycardias: As formerly said the occurrence of paroxysmal tachycardias is often associated with premature beats.

a.) Supraventricular paroxysmal tachycardias (SVPT): Two thirds of these arrhythmias afflict otherwise healthy men. Susceptible are mainly people with frequent SVPCs, WPW- and LGL-syndrome. The latter ECG-anomaly is a variant of the WPW-syndrome with short P-R intervaland narrow QRS-complexes.
Hemodynamic effects of these tachycardias are already significant in healthy hearts: The cardiac output decreases rate-dependent by 35 - 70 %, the average coronary flow by 35 %, the cerebral flow by 14 % (9, 10). Disturbing are also the subjective complaints of palpitations, fear and dizziness.

b.) Paroxysmal atrial fibrillation (PAF): The PAF is found relatively often in elder persons. It has been described also in younger asymptomatic individuals, even in pilots who returned to full flying status (5, 11), even so in an astronaut (2).
Premonitoring phenomena are like in SVPT frequent short coupled SVPCs and pre-excitation syndromes. The arrhythmia decreases the coronary flow by 30 %, the cerebral by 23 % dependent on ventricular rate and duration (9, 10). The affected person feels discomfort by the fast irregular heart rate, moreover the conversion from fibrillation to sinus-rhythm results not uncommonly in a larger asystole causing dizziness.
Besides the hemodynamic sequelae and subjective complaints with these arrhythmias also the clinical experience of insufficient response to drugs endangers the flying fitness. Moreover a therapeutic success is difficult to estimate because of their occasional, "paroxysmal" occurrence.

c.) Paroxysmal ventricular tachycardias (PVT): Though we have found like other authors (18) PVT also in asymptomatic people these individuals are jeopardized without detectable heart disease. These disturbances cause the most distinct decrease of cerebral blood flow with 40 - 75 %, of coronary flow with 52 % (9, 10). The possible change to ventricular flutter and fibrillation is even more fearsome. Interestingly in our series of outpatients PVTs were never triggered by R-on-T phenomenon but appeared without any harbinger.

Bradycardias: In cardiologically healthy persons bradycardias don't occur which alone reduce the cardiac output significantly. But due to certain reflex mechanisms the baroreceptors cause occasionally a drop of blood pressure and a bradycardia leading to fainting in predisposed persons, especially in young asthenic males. These men show often under vagal influence P-wave alterations, flattening or inversion without P-R shortening with decreasing heart rate (14). We found these rhythm disturbances like the A-V dissoziation, a wandering pacemaker and the junctional rhythm in the postpressor period of Valsalva-maneuver, during carotid and bulbus pressure, during squatting position likewise during rest and sleep.

Obviously persons with such variations of the resting ECG tend to faint with bradycardias. These symptoms can be triggered by mechanisms which can play a role also in high performance aircrafts. So cases of bradycardic syncope are described during high pressure breathing or testing of high pressure suits (24, 25). DERMKSIAN found bradycardias in 68 % of experimentally induced syncopes, 58 % of them by Valsalva-maneuver in erect position (12). FRANKE pointed out that a hyperactive carotid sinus in his group of 3500 individuals of all ages doesn't play a role before the 5th decade and warned to associate necessarily a positive response with cause of syncopes (17).
Also the first degree A-V block frequently found in healthy men (0,5 % of the flying personnel of the GAF, 10 % of our long-term ECG tracings in this group) has no prognostic implication. The same applies to the occasional occurrence of Wenckebach phenomena during rest and sleep. These blocking types are expressions of an overshooting vagal influence on the conducting system similar to the occasional short-termed S-A blocks.
In doubtful cases the atrioventricular conduction should be checked with intracardiac ECG registration methods under electrical or pharmacologic stimulation.
In this discussion it was felt not to elaborate on ectopic tachycardias or pathologic bradycardias which occur in the "sick sinus syndrome", the "prolapsed mitral leaflet syndrome" and the "bifascicular blocks". These dysrhythmias concern almost exclusively advanced ages and altered hearts.

Finally it should again be emphasized that especially in aviation medicine the appreciation of rhythm disturbances as possible normal variations without clinical significance has to be a diagnosis by exclusion. All diagnostic methods including invasive techniques like His-ECG registration and coronary angiography should be applied. Of great importance in our experience is therefore the principle of long-term ECG registration in these subjects, if possible also during flight; additionally continuous follow up examinations are suggested. A therapeutic approach with beta-blocking agents, particularly in special types of arrhythmias, may be sensible and is probably worth considering in the future.

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DISCUSSION

Triebwasser: You clearly illustrated rhythm disturbances in apparently healthy people that are similar to what you see in a patient population having organic heart disease. One problem we often see in young healthy people who have frequent ventricular premature beats is mitral valve prolapse. Do you return aircrewmembers to flying duties who have ventricular premature beats and mitral valve prolapse?

Dietz: No, I wouldn't. Aviators having mitral prolapse without rhythm or gross contractility disturbances probably can fly. But, with these disturbances no. I have seen many persons with mitral prolapse without rhythm disturbances.

Triebwasser: From a flying safety standpoint, how many ventricular premature beats are too many for a patient with mitral valve prolapse? For example, would you ground someone who has one on an eight hour recording?

Dietz: I can not say how many ventricular premature beats are dangerous. If there are only occasional ventricular premature beats and nothing else, you could return the pilot back to flying duties. Perhaps some medications such as the beta-blocking agents would be useful if there were no side effects.

In the coronary heart disease patient there is a figure of one to five beats per minute as being potentially dangerous and related to ventricular fibrillation.

Triebwasser: In the absence of an abnormal repolarization response, what do you do with a young pilot who has three consecutive ventricular premature beats at peak exercise?

Dietz: I would observe such a person over a period of one or two months. Perhaps he has myocarditis or another heart condition. If he remains healthy and has nothing other than ventricular premature beats during exercise, I see no risk to return him to flying duties. You see so many young people with ventricular premature beats under exercise. I don't see any implication.

Fitzgibbon: I think we are all plagued by these patients who have cardiac arrhythmias. In those which are obviously persisting and are not transient or evanescent, it is our policy with both supraventricular and ventricular arrhythmias not only to do noninvasive studies including procedures like echocardiography, but also to do invasive procedures including hemodynamic studies. We have found supine leg exercise preferable to supraventricular pacing. I wonder what your experience is with the use of hemodynamic studies in these cases? For instance, how many of your patients who have not had ventricular premature beats before, and who now develop them turn out to have a hemodynamic response to either supine leg exercise or supraventricular pacing which enables you to suspect a diagnosis of a cardiomyopathy?

Dietz: We haven't done hemodynamic studies with atrial stimulation in these patients. I don't believe a patient with atrial irritability is in danger. A more important question is what is the connection between coronary heart disease and arrhythmias? We have studied several of these people with coronary arteriography and didn't find a connection between coronary artery disease and all rhythm disturbances. For example, in atrial fibrillation, 30% of the patients had significant coronary stenosis and 70% had no stenosis, or other forms of heart disease. In the case of patients having ventricular premature 40% had significant coronary stenosis and 60% had no evidence for coronary disease. What I am saying is that when gross rhythm disturances exist, you should perform coronary arteriography but you often get no further information by this invasive method.

Fitzgibbon: This has been precisely our experience. I agree that supraventricular rhythm disturbances of themselves are not dangerous in the vast majority of cases, but simply are indicators of some potential underlying cardiopathy. We have found as you have, that to look for coronary artery disease in patients who present with cardiac arrhythmias is not a very hopeful journey. But we do find a very high incidence of abnormal hemodynamic studies highly suggestive of a cardiomyopathy. Now as I become somewhat older, I find myself becoming more and more suspicious of people who suddenly develop either supraventricular or ventricular arrhythmias than I was 25 years ago when I considered these things generally speaking, benign. We have found a group of patients who are very difficult to deal with because we found slightly abnormal left ventriculograms and an abnormal hemodynamic response to exercise with the left ventricular end-diastolic pressure rising to 24 to 26 mmHg. These people pose a very real problem from the standpoint of defining when one should ground them, always keeping in the back of ones mine that potentially lethal arrhythmias are a very common complication of cardiomyopathies of all types.

Dietz: I totally agree with you. Perhaps we should perform myocardial biopsies in these cases. Persistent atrial fibrillation precludes performing flying duties. Pilots having isolated rare bouts of atrial tachycardia or atrial fibrillation in the absence of heart disease could be returned to flying duties.

Triebwasser: It has been our observation that the majority of patients having frequent ventricular premature beats as a serial change, have an excessive alcohol and/or caffeine intake. If you can persuade them to stop smoking and to reduce their alcohol and caffeine intake, these will often disappear.

Leguay: You have mentioned beta-blocking agents. Do you believe it is advisable to give these beta-blocking agents to a fighter pilot who, for example, will be exposed to high acceleration forces?

Dietz: You have to make the decision of giving a beta-blocking agent individually for each person, but we have also found with hemodynamic studies that there is practically no negative ionotropic effect. The orthostatic reaction is not severe. I mean I could give them to a pilot and wait for the side effects.

DISTINGUISHING BORDERLINE HYPERTENSIVES FROM NORMOTENSIVES: A CLINICAL STUDY OF 300 AIRCREWMEN

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SUMMARY

Ambulant aircrewmen (299) referred to a clinical consultation service were evaluated with a brief orthostatic test; blood pressure (BP) and heart rate (HR) were recorded alternately during both supine rest and 5 minutes of quiet standing. The patients were divided into four groups depending on BP history (normotension vs. borderline hypertension) and BP from the current clinical examination (normal vs. elevated).

During supine rest, most patients with a normotensive history and a majority of those with a borderline hypertensive history had BPs in the normal range. During stand, BP remained normal in most normotensives but was elevated in a majority (62%) of borderline hypertensives. These results were used to compute the probability of borderline hypertension in an individual patient, given either the BP from his current clinical examination or the average BP from the stand part of his orthostatic test, or both. Curves were constructed showing this probability in populations with various prevalences of borderline hypertension. The value of an orthostatic test combined with a standard clinical BP in distinguishing between borderline hypertension and normotension is apparent.

INTRODUCTION

Blood pressure (BP) measurement is an important part of the routine physical examination. A single reading, supine or sitting, is usually all that is taken and recorded if that BP value is normal. When a borderline or frankly abnormal BP value is obtained, additional measurements are usually made with the "best" BP value (i.e., least abnormal) recorded for that examination. These additional readings may be supplemented by 3- or 5-day BP checks where multiple values are averaged to obtain a single "representative" BP for that patient. The ready acceptance of a first BP value when it is normal (although it could be an atypically low reading in a labile hypertensive), and the arbitrary approach used in the presence of an elevated BP value, both argue for an improved approach to the characterization of an individual's BP.

We felt dissatisfied with existing conventions for determining blood pressure in our aircrew population. Existing methods often seemed to deny or delay the diagnosis and, therefore, appropriate management of hypertension; or alternatively, might stigmatize the normotensive individual with an occasional "physiologically" high BP reading. Our earlier studies of orthostasis in borderline hypertension (1,2) suggested that a simple static stand test might distinguish the majority of borderline hypertensives from normotensives, and the present study was undertaken to discover whether this conclusion could be sustained with a much larger group of ambulant, largely asymptomatic flyers. We hoped to determine 1) whether any part of the response by borderline hypertensives differed significantly from that of normotensives, and 2) how this information might be used to differentiate between these two patient groups.

PATIENTS AND METHODS

The United States Air Force School of Aerospace Medicine (USAFSAM) provides a clinical consultation service for evaluating referred ambulatory military aircrew with suspected or manifest medical disorders. All patients in the present study were aircrewmen referred to this service; they were referred only if they were thought to have a reasonable chance of retaining or regaining flying status. Accordingly, obvious disqualifying conditions such as stroke, myocardial infarction, or malignancy were not seen; on the contrary, nearly all patients were asymptomatic, and most were referred for ECG changes or BP elevation detected at their routine annual physical examination.

Patients were selected for the present study between February 1976 and February 1977; initial patient selection was random, being based on patient availability within a busy clinical schedule. Later patient selection was biased in favor of hypertensives to improve the size of this group in our study. By February 1977, 343 patients had been tested. Data on 3 patients with sustained hypertension, 36 patients taking antihypertensive drugs and 2 taking digoxin, and 3 patients who fainted during the orthostatic test were removed from the data base. This left 299 patients for further analysis; either normotensive patients or patients with untreated borderline hypertension. Table I indicates the number of patients and the system supposedly implicated in their referrals.

TABLE I. MAIN CAUSE FOR REFERRAL OF 299 AIRCREW PATIENTS

Cardiovascular:		Neuropsychiatric	
ECG abnormalities and/or hypertension	133	Loss of consciousness	27
Other	49	Other	34
Ophthalmic and ENT	16	Gastrointestinal	7
Respiratory	10	Other	23

Blood pressure normality was defined as systolic blood pressure (SBP) below 140 mmHg and diastolic blood pressure (DBP) 90 mmHg or below (these are current USAF standards). The following patient groups were identified:

A. NORMOTENSIVE

1) BP normal by history and by present clinical examination (n = 231). These men denied a history of BP elevation or of requiring 3- or 5-day BP checks. Chart review confirmed BP normality for at least the past 5 years. The BP taken at the current clinical examination was also normal.

2) BP normal by history but elevated at present clinical examination (n =15). These men differed from those in Group A1 only because the BP from their current clinical examination was elevated.

B. HYPERTENSIVE

1) Borderline hypertensive by history but normotensive at current clinical examination (n = 19). These men all had records of one or more elevated BP readings on routine examination during the past 5 years, and many had undergone 3- or 5-day BP checks. None had sustained hypertension. Their BP from the current clinical examination was normal.

2) Borderline hypertensive by history and BP elevated at current clinical examination (n = 34). These men differed from those in Group B1 only in that the BP from their current clinical examination was elevated.

Orthostatic testing took place in the afternoon, at least 2 hours after patients had eaten. The test (Figure 1) involved a 10-minute period of supine rest (supine part) followed immediately by 5 minutes of quiet standing against the wall (stand part). Heart rate from the radial pulse and ausculatory BP (with diastole at cessation of sounds) were recorded on alternate minutes during the second 5 minutes of supine rest and the subsequent 5 minutes of standing. A quiet, air-conditioned room was used for all testing, with only the patient and one technician present. Restful conditions were ensured by a closed door, absence of a telephone, and proscription of all conversation. The majority of tests were conducted by two technicians who were shown by audiometry to have normal hearing. Procedures were standardized by the use of printed instruction sets.

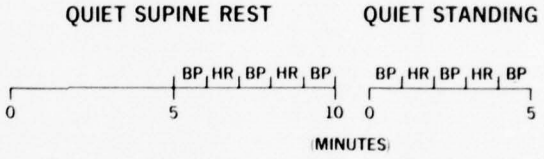


Figure 1. The orthostatic protocol is shown. Supine rest (supine part) was followed immediately by quiet standing (stand part).

The casual BP value obtained by the examining physician at the current USAFSAM clinical examination and measurement data from the orthostatic test were all entered into a computer for subsequent reduction and manipulation. For each patient, means of SBP, DBP, and HR values from the supine and stand parts of the orthostatic test were computed; these mean measurement values from the two parts of the test were used for all subsequent analyses and presentation.

RESULTS

The BP findings from both parts of the orthostatic test are presented in Table II. For the supine part of the test, normal BPs were recorded in almost all Group A (normotensive) patients (244 of 246), and in a majority (41 of 53, 77%) of the Group B (hypertensive) patients. The supine part of the test therefore correctly identifies nearly all normotensives but fails to recognize most hypertensives; in formal terms, the supine part shows a low sensitivity (23%) but a strikingly high specificity* (99%).

During the stand part of the test, hypertensive BPs were recorded in 8.1% of Group A (normotensive) patients. Hypertensive responses increased to 37% of Group B1 and to 76% of Group B2 patients--an overall 62% positive rate for all Group B (hypertensive) patients. The sensitivity of the stand part of the test was thus 62%, and the specificity was 92%.

*Footnote. The sensitivity of a test is the measure of its capacity to detect an abnormality. A highly sensitive test will detect nearly all abnormal individuals. Sensitivity is expressed as the fraction, true-positives divided by true-positives plus false-negatives.

The specificity of a test is the measure of its capacity to recognize normality. A highly specific test will be negative in nearly all normal individuals. Specificity is expressed as the fraction, true-negatives divided by true-negatives plus false-positives.

Sensitivity and specificity are independent of the prevalence of an abnormality in the sample tested and therefore will remain valid where bias or selection distort the composition of a sample.

TABLE II. BLOOD PRESSURE FINDINGS IN ORTHOSTATIC TEST

	A. Supine Part					B. Stand Part				
	Normal	Elevated				Normal	Elevated			
		SBP	DBP	Both	Total		SBP	DBP	Both	Total
Group A1 (n = 231)	231	0	0	0	0	214	1	15	1	17
Group A2 (n = 15)	13	2	0	0	2	12	0	2	1	3
Group B1 (n = 19)	19	0	0	0	0	12	1	6	0	7
Group B2 (n = 34)	22	8	2	2	12	8	6	12	8	26

The number of patients showing normal or elevated blood pressures during the orthostatic test (subdivided into supine and stand parts) is presented by patient groups.
Composition of each group is defined in the text.
Orthostatic test BPs = Mean value of 3 readings

The physician, however, deals with an individual patient and must therefore estimate the probability of a diagnosis using available clinical and test results. Assuming a) the validity of an historically-defined patient classification and b) that the prevalence of borderline hypertension in the patient's population can be estimated, we can use our data to develop predictive functions for this purpose. Probability of borderline hypertension has been calculated for a) the case where a current clinical BP is the sole item of information available, b) the case where an orthostatic test response is the sole item of information available, and c) the case where both items are available. All three cases assume that the medical examiner has no knowledge of the patient's BP history.

Figures 2-5 show the results of our probability calculations. The lower two curves in Figure 2 show that the likelihood of borderline hypertension is similar (and considerable), given the sole finding either of an elevated clinical BP or of an abnormal stand response. For example, if the community prevalence of borderline hypertension is 20%, an elevated clinical BP or an abnormal orthostatic test means that the patient has a 60% chance of being hypertensive. When the elevated clinical and test BPs are combined, the likelihood rises to over 90%. As noted, the likelihood rises as the prevalence increases. The middle curve in Figures 3 and 4 shows the corresponding probabilities when the results of clinical BP and orthostatic test are conflicting. The effect is substantially to reduce the significance of a single positive finding. Conflict between clinical BP and orthostatic test, which occurred in 44 (15%) of all our patients, would suggest caution in diagnosis and the need for further evaluation. Figure 5 shows the probabilities of hypertension when there is a normal clinical BP or normal orthostatic test (stand part), or both. The gain from combining clinical BP and test (lower curve) is useful though modest.

DISCUSSION

A number of authors have described a "hyper-reactive" response to orthostatic stress in borderline hypertensives (3,4,5); these studies have typically involved the use of invasive techniques, and their borderline hypertensives showed an excessive rise in mean BP during short-term tilting. However, Esler and Nestel (6), using ordinary sphygmomanometry, found a "hypertensive" diastolic rise in DBP of 11 mmHg or more in 10 of 41 hypertensive patients, and these diastolic "hyper-responders" (most of whom also showed an orthostatic rise in SBP) were on the whole the mildest hypertensives. This excessive orthostatic increase in blood pressure in many borderline hypertensives has been generally regarded as evidence of a strong neurogenic factor in the disorder; the rise occurs early, within a minute of assumption of the upright posture, and is often accompanied by other features such as an excessive rise in urinary norepinephrine (6) and plasma renin activity (7,8). Borderline hypertensives may show a wide variety of resting hemodynamic abnormalities when supine (9,10,11). With head-up tilt, there is often an excessive fall in cardiac (3) and stroke (5) indices and an excessive rise in peripheral resistance (12) and in heart rate (13) compared with normotensives. A hypertensive orthostatic response is therefore likely to be one manifestation of the autonomically sustained abnormal circulatory state demonstrable in a substantial number of borderline hypertensives.

In our earlier orthostatic stress studies (1,2) we found that most borderline hypertensives had normal blood pressures during supine rest, but the majority (71%) showed diastolic hypertension during orthostasis. This effect was not seen in normotensive controls. The present study has again shown that a majority of patients with a history of borderline hypertension show normotensive BP levels after a brief period of supine rest, but that orthostatic stress causes a hypertensive response in a small majority (62%). In other words, the sensitivity of the stand part of the test is 62%; a result of moderate usefulness, similar in our sample to the sensitivity of an elevated clinical BP (64%). Combining the test and the clinical BP results does not increase sensitivity.

However, by analyzing our results in a different way, to calculate the probability of hypertension in an individual patient, the value to the clinician of the combined findings of a clinical BP and stand part of the test can be considerably increased, provided that an estimate of the population prevalence of borderline hypertension can be made. Under these circumstances, when clinical BP and the test are concordant, as they were in 85% of our patients, a diagnosis of hypertension or normotension can be made with 90% confidence, assuming a 20% or greater prevalence of borderline hypertension which is probably

Figure 2

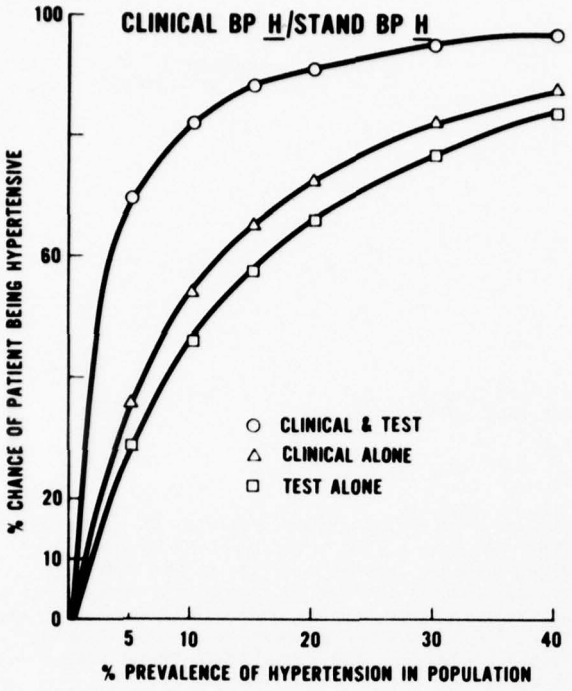


Figure 3

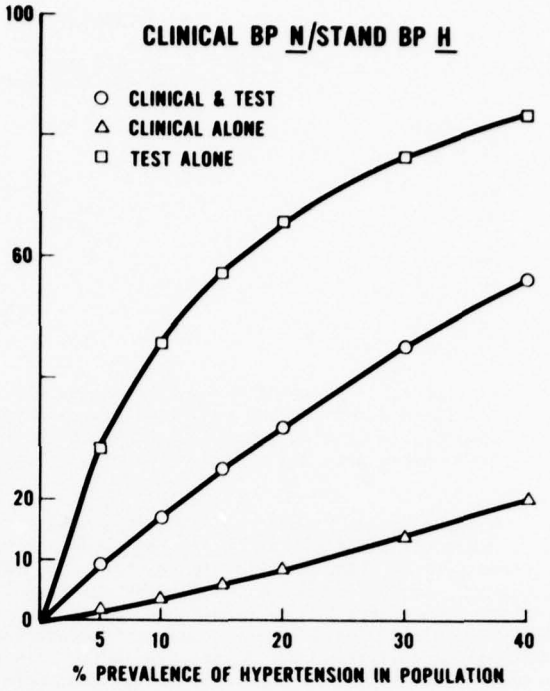


Figure 4

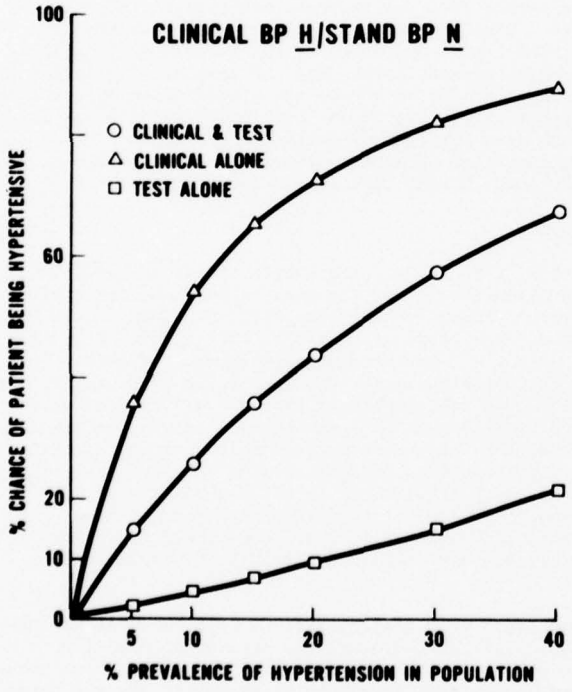
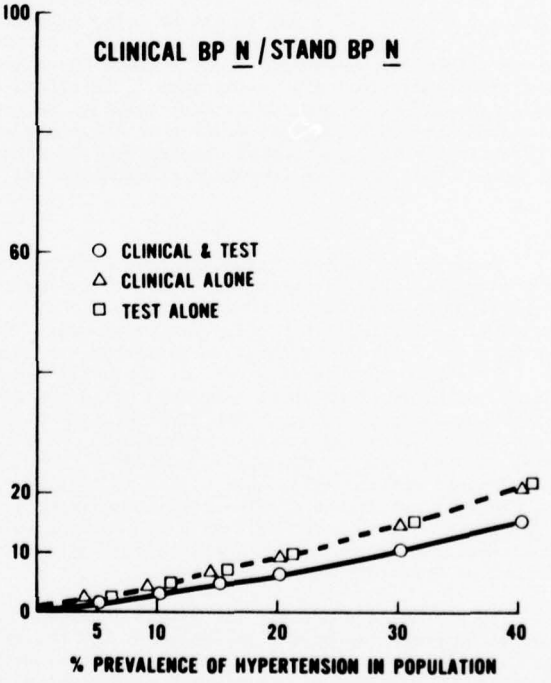


Figure 5



Figures 2-5

These figures show how the likelihood (as % probability, ordinate) of a patient's having borderline hypertension is related to the population prevalence of that disorder (abscissa). The four possible combinations of current clinical BP, normal or elevated, and stand part of orthostatic test, normal or abnormal, are presented. In each figure, curves indicate the likelihood of borderline hypertension a) if current clinical BP only is known, b) if stand part of orthostatic test only is known, c) if both items are known. (In Fig. 5 the dotted line indicates near-identity of a) and b)).

H, Hypertension, Hypertensive = Borderline ditto.

N = Normotensive.

usual in most Western communities. We, therefore, believe that a brief orthostatic test can reliably distinguish borderline hypertension from normotension in the great majority of patients. We commend this test to all those concerned with the diagnosis of borderline hypertension.

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APPENDIX

The percent probability of an individual patient being hypertensive, given the prevalence of hypertension in his population, and given a specific outcome of his clinical and/or stand part of his orthostatic test, is computed from the quantity:

$$\frac{hp}{hp + n\,(100-p)} \quad X \quad 100$$

where: h = percent of hypertensives showing a specific outcome
= (# of hypertensives with outcome/total # of hypertensives) X 100

n = percent of normals showing that same outcome
= (# of normals with outcome/total # of normals) X 100

p = percent prevalence of hypertension in the population to which the individual belongs.

NOTE: h and n are estimates computed from our observed data sample.

EXAMPLE: For a given individual, we observe the following:

clinical BP = N

stand BP = N

Let us assume he comes from a population where the prevalence of hypertension is 20% (i.e., p = 20%)

From our data sample (Table II), we can estimate h and n for the outcome observed (N, N):

$$h = \frac{\#\text{ hypertensives with N,N}}{\text{total \# hypertensives}} \quad X \quad 100 = \frac{12}{53} \quad X \quad 100 = 22.6\%$$

$$n = \frac{\#\text{ normals with N,N}}{\text{total \# normals}} \quad X \quad 100 = \frac{214}{246} \quad X \quad 100 = 87\%$$

∴ The probability of the individual being hypertensive, given his test outcomes (clinical = N, stand = N), is:

$$\frac{hp}{hp + n\,(100-p)} \quad X \quad 100 = \frac{22.6\,(20)}{22.6(20) \;+\; 87(100-20)} \quad X \quad 100 = 6.1\%$$

Proof of Formula:

Suppose we have a population where:

p = the % prevalence of hypertension in that population

r = number of subjects in population

Then it follows that:

r_H = pr/100 = # of hypertensives in population

and r_N = (100 - p)r/100 = # of normals in population

If our estimates of h and n from our present data sample are good for a specific outcome, then

$h(r_H)/100$ = # of hypertensives in population that will show the specific outcome

and $n(r_N)/100$ = # of normals in population that will show the specific outcome

Therefore:

$h(r_H)/100 + n(r_N)/100$ = total # of subjects in population that will show the specific outcome.

The percent of those showing the outcome that are hypertensives is therefore:

$$\frac{h(r_H)/100}{h(r_H)/100 + n(r_N)/100} \times 100$$

$$= \frac{h(pr/100)/100}{h(pr/100)/100 + n\{(100-p)r/100\}/100} \times 100$$

$$= \frac{hp(r/100^2)}{hp(r/100^2) + n(100-p)(r/100^2)} \times 100 = \frac{hp}{hp + n(100-p)} \times 100$$

Q.E.D.

DISCUSSION

Pröhl: Hypertension is one of the most common problems we have to cope with. I thank you for giving simple means to increase the accuracy of our diagnoses in borderline cases. Now from a practical point of view, what's your attitude in the case of confirmed hypertension in pilots flying single seat, high performance aircraft with a diastolic pressure, which I think is the more important, beyond 95 mmHg and who have a normal eye fundus and normal renal function? Would you keep them in flying status in high performance aircraft?

Hull: The United States Air Force regulations suggest that they should not remain on flying status with that type of blood pressure, particularly if it were repeatedly discovered to be elevated, unless it could be satisfactorily treated and completely controlled with an acceptable preparation, which until now has been a diuretic preparation. So the attitude is that the disorder is safe provided it is adquately controlled.

Pröhl: And would you keep him on flying status with the diuretic treatment?

Hull: Yes, the policy is to observe them on the ground for periods of time which is somewhat arbitrary, but usually six to eight weeks, to see first of all whether the treatment is effective and secondly, whether any side effects are occurring. Provided these conditions are favorable, the pilot is frequently granted a waiver to return to flying duties.

Triebwasser: As Dr. Hull stated this is our present policy, but we need to reconsider it in terms of the high performance aircraft pilot. It could be argued that if this man does not have any end-organ disease, he might be better off untreated in terms of his performance in a high performance aircraft because a diuretic agent might diminish his G-tolerance. We have no evidence for that in our studies examining G-tolerance as Dr. Hull described earlier in this meeting, but we haven't tested this in the high $+G_z$ stress environment. Your question is an excellent one. We are always uncertain as to how one should handle a hypertensive pilot. For example, when should you start treatment? I think most of us would agree that everybody should be treated if their blood pressure is greater than 160/100 mmHg. But, what about the individual whose diastolic blood pressure is between 90 and 100 mmHg? We have no proof that treatment in the latter case is beneficial. However, there is more and more evidence accumulating that treatment should be beneficial in this population. To be honest, I'm sure most of us are influenced by family history, and physical and laboratory findings suggesting end-organ involvement. These things dictate when we start to employ drug therapy on a clinical basis, but in the case of the aircrewmember we have published standards. We have arbitrarily taken the role of treating all individuals whose blood pressure has exceeded these standards. Although this is very controversial, I believe early treatment is beneficial and should be employed, especially when one can use a relatively benign agent such as a thiazide diuretic. More importantly, we must bear in mind that drug therapy should not be used instead of weight reduction and sodium restriction.

Leguay: With regard to hypertension, we believe that it should be treated as soon as it begins to manifest itself, because we have found that some pilots, whose flying fitness had been slightly neglected, did have accidents. Consequently, one takes a great chance by not treating incipient hypertension, especially in combat pilots. We treat them essentially with diuretics, and we check two aspects: 1) orthostatic hypotension, and 2) a centrifuge run up to 5 G's without a pressure suit. These are our requirements to maintain pilot fitness.

Hull: Yes, thank you very much but I'm sure that that is entirely in accord with our practice both in the Royal and the United States Air Forces.

McIntyre: Your group B1 interests me, the group that had hypertension and now is normal. What do you think is the prognosis of these so called labile hypertensives? Do you do anything special for them?

Hull: This is difficult because in fact, in a real sense, all these subjects were labile hypertensives. None of them had fixed hypertension, and that classification was based simply on the findings at one current examination. In fact, I think it's axiomatic that some would fall into B1 and then into B2, and that is just the proportion that we happened to find. With a different group of patients we might find rather different proportion, and it is extremely difficult because nobody wants to wait for fixed hypertension before treatment. The majority of aircrewmen that we treat would be characterized as borderline or labile hypertensive, and I think probably the majority of these are better off on treatment, provided that treatment can be given without causing side effects.

MOLECULAR DETERMINANTS FOR THE PREDICTION AND SURVIVAL OF ISCHEMIC ANOXIC STRESS PATHOLOGY

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SUMMARY: Quantitation of membrane phospholipids in mitochondria and microsomes from acceleration stressed as well as radiation stressed animals revealed significant variations in individual species of phospholipids which were reiterated in the blood plasma. Application of this methodology to humans showed the feasibility of achieving a molecular index to stress via blood plasma phospholipids. These results were complimented with studies for non-invasive procedures using the techniques of high pressure liquid chromatography and electron spin resonance spectroscopy to detect excited state metabolites in urine which could be correlated with stress intolerance. With this procedure a significant increase in free radical forming species was found in the urine of volunteers centrifuged to grayout as well as in a civilian population of patients scheduled for heart surgery. Correlation of the free radical concentrations with values for lipid peroxides and phenolic compounds gave a three dimensional readout which separated stress tolerant individuals from those with debilitating intolerance to stress.

In the course of studies on the bioregulatory factors of energy transducing systems, it was realized that brain activity in-vivo and oxidative phosphorylation in-vitro could be modified by molecules in a stable free radical state. In attempts to synthesize a structure which could react with lipoprotein sites in energy transducing membranes, a stable free radical polymeric derivative of prostaglandin B was discovered with the unique properties of conserving the ability of mitochondria to phosphorylate oxidatively under degenerative conditions that destroyed phosphorylation efficiency. The same compound, called PGB_X, markedly enhanced the survival of monkeys in cardiogenic shock from an induced myocardial infarction with fibrillation. In similar fashion, rabbits subjected to global ischemia by tying the vertebral arteries and both carotids to produce electrical silence for 20 minutes and then releasing the carotid tie, had a complete recovery in seventy percent of the animals treated with PGB_X compared with a thirty percent recovery with neurological damage in the controls.

These findings indicate the feasibility of detecting the onset of incipient pathology from stress intolerance and the practicability of the molecular intervention to revoke the fatal prognosis of ischemic anoxic crises.

INTRODUCTION

Experiments with isolated mitochondria and microsomes from tissues of stressed rats suggested ischemic anoxic crises arose from a sustained demand for biological energy under conditions of limited supply to the point of exhaustion of adaptive mechanisms and the onset of pathology (1,2). It was expected that these events would be presignaled by molecular changes which reflected biomembrane regulatory mechanisms pertinent to the bioenergetic pathways involved. These molecular changes also might afford a predictive index or end point to stress tolerance and implicate critical functional sites for a molecular intervention to enhance survival of a crisis state.

Variations in tissue phospholipids from animals and plasma phospholipids from humans exposed to physical and mental stress confirmed the premise that common biochemical components are mobilized by diverse physiological reactions to stress. Almost identical changes in the plasma levels of phosphatidyl glycerol were obtained in rats accelerated to 20G and in humans accelerated to grayout. Similar elevated levels of phosphatidyl glycerol were found in humans subjected to sleep deprivation, combat flying or in patients hospitalized with the diagnosis of chronic schizophrenia. These stressed populations could be differentiated from each other statistically by the additional changes in other phospholipids (3).

Molecular Correlates of Stress Intolerance

Procedural difficulties in adapting the phospholipid methodology for field use emphasized the need for and advisability of a non-invasive rapid and simple objective molecular index for the exhaustion of adaptive reserves and the onset of debilitating mental and physical states. To this end urine samples from populations under control and stress conditions were subjected to high pressure liquid chromatography and electron spin resonance spectroscopy seeking for molecular changes uniquely correlated with the stress. The free radical forming molecules in urine are detected in chloroform-methanol (10%) made alkaline with tetraethylammonium hydroxide. Originally urine from control and stressed subjects was partitioned between the organic and water phases of chloroform-ethanol-water (4:2:3) mixtures to remove cationic solvent soluble components and neutral lipids. The water soluble phase was then acidified to pH 2.5 and extracted into isobutanol. After concentration by evaporation of the solvent, the fraction was analyzed by ESR. Subsequently Dr. H. Shmukler developed a simple procedure for concentrating the free radical forming (FR) compounds by percolating the urine through a column of XAD-2 resin. After washing with water to remove the inorganic salts and unadsorbed organic compounds, the FR compounds could be eluted with methanol. Chromatography of this eluate showed that the FR compounds were not a single species but comprised representative species of classes of metabolites which either were in free radical form or could be converted to a free radical by proton abstraction.

With this procedure a significant increase in FR molecules was found in the 24 hour urine of volunteers centrifuged to grayout when compared to the concentrations found in the 24 hour urine before acceleration. The differences were significant at the 1% level of confidence. Although in itself the FR content seemed to have little predictive significance, when the differences in free radical content pre and post acceleration were plotted against the highest G tolerated by the subject, an inverse correlation of G tolerance with FR signal detected became manifest, i.e. the individual with the lowest G tolerance

and the most problems in the group had the highest ESR signal in his urine. Those subjects with the greatest tolerance and best performance had the lowest signal (Fig. 1).

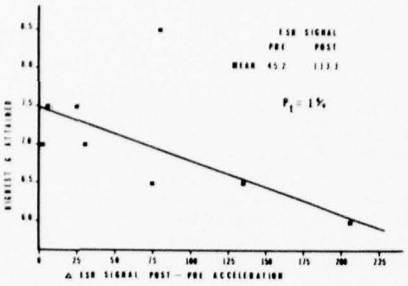

Fig. 1. Correlation of Free Radical Components in Urine with Acceleration Tolerance.

The rate of onset of all runs shown in fig. 1 was 3.5G. The duration of the G plateau was 15 seconds followed by a decay rate of 2.5G/sec. G levels were increased in increments of 0.5G for each successive run up to peripheral light loss. Twenty-four hour urine samples collected pre and post acceleration were analyzed as described in text.

The group studied after centrifugation was essentially young, in normal good health and obviously had survived the physical stress. The most drastic aberration observed was a low tolerance to acceleration and an emotional inability to cope with the Navy environment. Both correlated with the high output of FR in the urine. To extend the population studied to a more general group in life threatening situations we chose a group of patients scheduled for cardiac surgery and hence presumably stressed both by tissue anoxia and by anxiety. In contrast to the centrifuged group, all the patients scheduled for heart surgery showed a high FR content in the urine before surgery. This significantly decreased within 48 hours after successful surgery. There obviously was good correlation between stress and the FR content of urine. But a more discriminating and predictive index was desired not one merely correlative with stress but indicative of a debilitating functional reaction to the stress. This we sought to achieve by evaluating class reactions of compounds found in higher concentrations in stressed subjects by high pressure liquid chromatography.

The results of these studies carried out by Dr. H. Shmukler of this laboratory are illustrated in the three dimensional plot of fig. 2. The three axes represent the free radical concentration in arbitrary units corrected for dilution to 24 hour volume output; the lipid peroxide content as measured colorimetrically by reaction with thiobarbituric acid (4) and the phenolic compounds assayed by the photometric density of the reaction with diazotized p-nitroaniline (5).

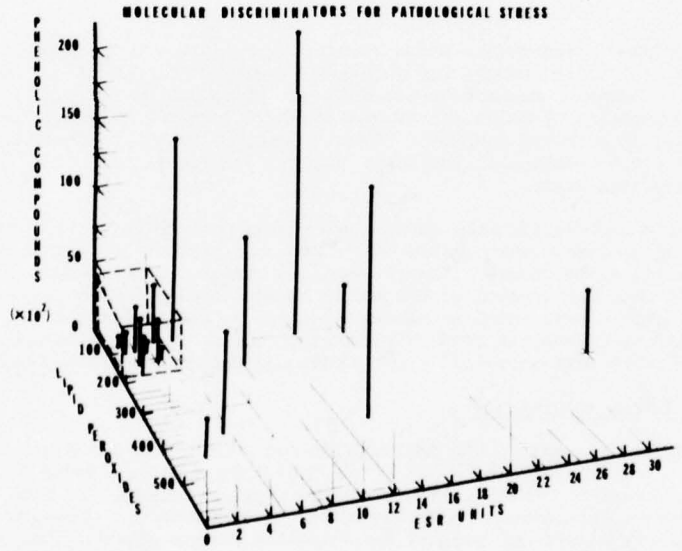

Fig. 2. Three dimensional plot of Free Radical content, Lipid peroxides and Phenolic compound content of 24 hour urine to discriminate normal and stress tolerant subjects from stress intolerant patients. Each line position represents an individual subject.

The result of the plot is that all normal subjects and those cardiac surgery patients who staged an uneventful recovery are concentrated in the small boxed volume near the origins. The eight patients outside this volume represent one patient who died post surgery and seven others who recovered physically sufficient to be discharged but were seriously disturbed emotionally to the point of being functionally disabled.

The ultimate objective of these studies is to define the biomolecular mechanisms of debilitating stress so that an objective index of approaching intolerance limits may be predetermined and protective measures instituted to enhance performance and survival. The immediate aims are to isolate and identify those molecular constituents of body fluids which are correlative with stress intolerance and to develop methods for rapid and specific detection suitable for field use. The data presented shows the feasibility of the

ultimate goals of the program.

IN-VITRO CONSERVATION OF OXIDATIVE PHOSPHORYLATION IN-VIVO SURVIVAL OF ISCHEMIC ANOXIC CRISIS WITH PGB_X

There is now increasing evidence that the consequences of tissue ischemia and anoxia leading to cellular catastrophe and eventual death can be related to biochemical abnormalities with decreased adenosinetriphosphate (ATP) production, mitochondrial damage, changes in membrane permeability, lysosomal membrane rupture, cell damage and finally death. Myocardial cell death is believed to occur when intracellular ATP drops below 2.0 μmoles/gram and the anaerobic metabolism of the ischemic heart stops. The major synthesis of ATP in the mammalian cell occurs in mitochondria. It follows that any attempt to improve the survival of ischemic anoxic crises must first retain or restore oxidative phosphorylation in mitochondria.

For a model in-vitro system mimicking the state of an ischemic cellular catastrophe a procedure was developed whereby rat liver mitochondria, isolated in 0.3 M sucrose - 0.0005 M versene, are selectively degenerated by ageing in sucrose at 0^{0}C. Subsequent incubation at room temperature with α-ketoglutarate, phosphate buffer and Mg^{++} in the absence of added nucleotide causes a complete loss of phsophorylation activity. Studies of various molecular structures for the conservation of oxidative phosphorylation under these degenerative conditions led to the synthesis of the polymeric, stable free radical derivative of 9,15-diketo prostaglandin B_1 called PGB_X. This base catalyzed condensation product of the original monomer is a tetramer with molecular weight ~1500, has completely different physical chemical properties (UV, IR, NMR, ESR) from any of the conventional prostaglandins, and has none of their characteristic pharmacological activities. With intact, coupled mitochondria PGB_X has no discernible effect. Nor has any apparent effect been found on administration of PGB_X to normal animals. In this respect PGB_X seems to act like a coenzyme added to a saturated enzyme system or a vitamin given to a normal healthy animal. When added to mitochondria under degenerative conditions the recovery of phosphorylation efficiency is dramatic. Similarly when PGB_X is administered to an animal in cardiogenic shock or one suffering cerebral anoxia from an induced global ischemia, the recovery was equally dramatic. (6)

The curves illustrated in figs. 3 and 4 represent the inorganic phosphate converted to ATP in a 20 minute reaction time after the preliminary degeneration run for the indicated time intervals. The control run without PGB_X represented by the broken line, is the μmoles of phosphate esterified directly. The solid line (PGB_X) represents the phosphate esterified with PGB_X minus the phosphate esterified in the control under the same conditions. It is then evident that with no degeneration or degeneration up to 5 minutes PGB_X has no significant effect on the oxidative phosphorylation in the intact mitochondria. As the mitochondria is degenerated from the 10 minutes reaction on, PGB_X counteracts the damaging effect and phosphorylation is maintained at normal levels. A similar effect of PGB_X is observed with mitochondria aged for 4 days at 0^{0}C, except that degeneration takes place much faster with the Mg^{++} catalyzed inactivation and PGB_X recovery becomes manifest more rapidly. Fig. 4 shows the titration of a degenerate system with increasing concentrations of PGB_X. Kinetically the S shaped curve may be interpreted as representative of a multiple site activation of mitochondrial phosphorylation by PGB_X. In the range up to 2μg/reaction the sites are unfilled and there is little or no effect of PGB_X on ATP formation. From 3μg/reaction on, the mitochondrial sites are rapidly filled by PGB_X and activity rapidly reaches a maximum. This type reaction is also known as a trigger mechanism effect or all or none reaction and is characteristic of switching or control kinetics.

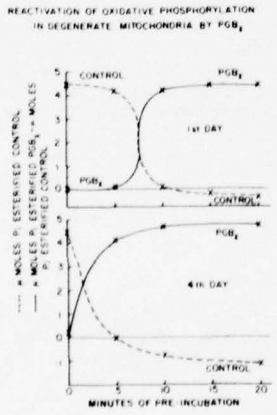

Fig. 3. Conservation of Oxidative Phosphorylation in Degenerating Mitochondria by PGB_X

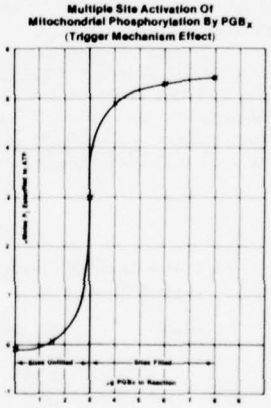

Fig. 4. Multiple Site Activation Kinetics of Mitochondrial Phosphorylation Induced by PGB_X in Degenerated Mitochondria

Reactions are carried out in 2.0ml of solution containing 0.1ml of 0.1 M phosphate buffer pH 7.4, 0.15ml of 0.2 M α-keto glutarate, 0.1ml of .1 M $MgSO_4$ and 4mg of mitochondria incubated in a shaker bath at 27°C for the stipulated times for degeneration. At the end of the inactivation period mixtures of ADP,AMP, KCl and bovine crystalline albumin are added to both control and PGB_x containing reactions. Final concentrations of reagents are 0.005 M $MgSO_4$, 0.045 M KCl, 0.005 M PO_4, 0.014 M α ketoglutarate, 0.0023 M ADP, 0.0023 M AMP and .07% albumin in a final volume of 2.2 ml at pH 7.4. The reaction is terminated by the addition of 0.5ml of cold 31% $HClO_4$. The protein precipitate is centrifuged down and the inorganic phosphate remaining in the supernatant is analyzed by measuring the absorbance of the extracted phosphomolybdate (7). Concentrations of ATP, ADP and AMP in the reaction mixture are determined by the high pressure liquid chromatography procedure for nucleotides by Shmukler (8).

It was therefore, conclusively demonstrated that under conditions which inhibited oxygen uptake and completely blocked the ATP synthesis of mitochondria, PGB_x restored both oxygen uptake and ATP synthesis to normal levels. In studies with inhibitors and Ca^{++} competing for phosphorylation sites on the mitochondria, the effect of added mitochondria was to direct the reaction toward synthesis of ATP and increased efficiency of phosphorylation. This effect, however, became evident only with damaged mitochondria. These findings suggested the application of PGB_x to the problems of survival following acute ischemic anoxic crises in heart and brain.

With Prof. E. T. Angelakos, an experimental program was devised to evaluate the effect of PGB_x in the restoration of heart function in monkeys, after lethal periods of ischemia and hypoxia had rendered the organ intractable to the most effective therapeutic procedures prevalent (9). This involved evaluation of cardiovascular recovery after a period of ventricular fibrillation in heart with a left ventricular infarction from a coronary ligation. This insult was of such magnitude that recovery was at best difficult and a high incidence of mortality the general finding. Ventricular fibrillation, which occurred spontaneously or was induced electrically within 20 minutes after ligating the left descending coronary artery, was continued for specified times ranging from 4 to 24 minutes. After the specified time, resuscitation procedures were started which consisted of intracardiac injection of norepinephrine, cardiac massage and electrical defibrillation. If electrical and contractile activity of the heart were reestablished, the monkey was allowed to recover spontaneously. If the animal remained in shock norepinephrine was infused intravenously until the animal attained a blood pressure over 40/20 mm Hg or became refractory to norepinephrine and died. If the monkey recovered from the first 4 minutes fibrillation and became stable for a period of 20 to 30 minutes, the monkey was subjected to the next higher fibrillation period of 6 minutes. In this manner the monkeys were subjected sequentially to episodes of fibrillation of 4, 6, 8, 12 and finally 24 minutes duration with 20-30 minute recovery periods until the animal died in shock or successfully survived the course. The monkeys treated with PGB_x were injected with 1mg/Kg intraventricularly after the norepinephrine and before electrical defibrillation. This procedure applied to 32 monkeys (16 controls) resulted in 60% survival of the controls and 100% survival of PGB_x treated animals after the 4 minute fibrillation. Only 25% of the controls but 88% of the PGB_x group survived the cumulative fibrillation of 30 minutes. Five out of six of the PGB_x treated animals and none of the controls survived the 54 minute cumulative fibrillation run. The differences were markedly significant statistically.

With the successful recovery from cardiogenic shock by PGB_x therapy we turned our attention to ischemic anoxic episodes in brain. For this study an experimental model was devised with rabbits during a collaborative effort with Dr. R. Kolata at the University of Pennsylvania. In brief the methodology involved clamping the two vertebral arteries and the insertion of ties around the two carotids while the animal was under halothane anesthesia. With injections of Arfonad and titrated infusions of norepinephrine the rabbit was maintained in a hypotensive state with blood pressure at 85/55 mm Hg. With the rabbit instrumented to record EEG, ECG and blood pressure, the animal was placed under positive artificial respiration and the carotid ties tightened to produce complete global ischemia. The EEG became flat within 35-45 seconds and remained silent for 20 minutes. At the end of this time PGB_x was injected into the treated rabbits and the carotid ties released in both treated and control animals. Blood pressure was maintained in both groups of animals by small infusions of norepinephrine intravenously if necessary to keep the animals out of shock. The animals were monitored until EEG activity and spontaneous respiratory control returned and the animals began to struggle against their restraints or until they died. PGB_x was given to the rabbits at the rate of 1mg/Kg every hour for the first 4 hours or until the rabbit was upright and alert. Those rabbits that were alive after 48 hours were termed survivors. Comparisons of the survivals of control and PGB_x treated rabbits are shown in fig. 5.

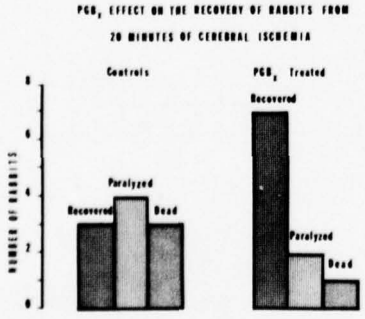

Fig. 5. PGB_x Effect on the Recovery of Rabbits from 20 minutes of Cerebral Ischemia.

The data of the in-vitro and in-vivo studies implicate PGB_X in energy transfer mechanisms across biological membranes. The observed effects might be explained on the basis of some esoteric membrane conformational changes or even as the doping of a lipoprotein semi-conductor system with a lowering of activation energies to pump electrons into a conduction band. However, the free radical properties of PGB_X and the indications of intermediates of labelled reactions suggest the involvement of PGB_X as a bridge between electron transport and phosphorylation mechanisms. Although the mitochondrial reactions do not necessarily define all the in-vivo effects of PGB_X the result offer a new and unique approach to enhance survival in conditions of impaired perfusion of heart and brain.

The observation that the synthetic product PGB_X only became effective in damaged mitochondria or in severe anoxic pathology of the whole animal suggested that PGB_X was replacing or by-passing a natural constituent of cell membrane important in the transfer of biological energy. To investigate this point mitochondrial membrane proteins were acidified and extracted into isobutanol. Evaporation of the solvent and separation of the lipids by molecular exclusion and reverse phase chromatography yielded a product with the in-vitro properties of PGB_X on phosphorylation recovery, except that it took 4 times as much material as PGB_X to achieve the same level of phosphorylation recovery.

This suggested that in incipient pathological conditions a factor similar to PGB_X might be released from damaged tissue and appear in the urine. To test this hypothesis 20 liters of urine from patients scheduled for heart surgery were processed through the chromatography procedures for isolation of urine free radicals and purification of PGB_X. Almost 200 micrograms of a compound (still not pure) was recovered which had properties identical to PGB_X in conserving ATP in degenerate mitochondria (fig. 6).

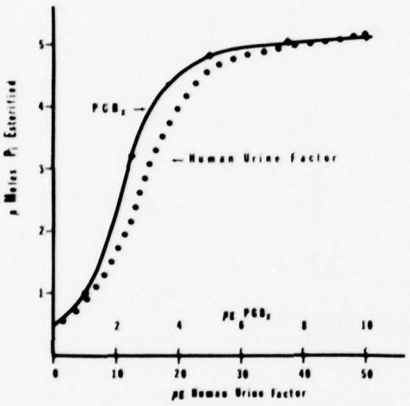

Fig. 6. Comparison of PGB_X and Isolated Human Urine Factor in the Conservation of Oxidative Phosphorylation in Degenerating Mitochondria.

These studies provide a rational theory for the use of PGB_X in replacement therapy for the ischemic cellular damage in heart and brain incurred during myocardial infarction and cerebral vascular accident and offer a new approach for the early detection of cellular damage in humans. This is especially feasible since the structure of PGB_X and its naturally occurring counterpart lends itself to the formation of antibodies and therefore to radio-immuno-assay procedures. It is expected that this specific factor assay coupled with the free radical correlates described will offer the definitive stress end point sought. As a bonus for civilian use the technique should provide early warning signals of impending heart attacks or strokes and serve as a control monitor for therapy.

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PSYCHOSOCIAL ASPECTS OF SYNCOPE AND VERTIGO IN AIRCREW

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SUMMARY

For an 8.5-month period, all cases (N=47) referred to the USAF School of Aerospace Medicine for evaluation of syncope, vertigo, or dizziness were seen for a standardized psychiatric interview, mental status examination, hyperventilation experience, and psychometrics. Twenty-one patients reported that their symptoms of hyperventilation were the same as or very similar to their reference symptoms. The findings from this subgroup were analyzed and compared to a group of 31 control subjects. The study group reported a great deal more symptoms after hyperventilating (a checklist was used). They were much more apt to report job maladjustment, parental conflict, and separation from their families. Common mental status findings were low self-esteem, worry, helplessness, fearfulness, suspiciousness, evasive-guardedness, meticulousness, and perfectionism. Their prominent mental defense mechanisms included projection, intellectualization, and repression. The Cornell Index and Cattell's 16 PF showed significant group differences.

INTRODUCTION

Sudden incapacitation of aircrew is dreaded by all. Perhaps the epitome of this anathema is loss of consciousness (LOC). Great effort is given to selection and retention of aircrew without risk of seizures or fainting. If LOC occurs, the airman is grounded. He is returned to flying only after thorough clinical study and only if the event was clearly explainable, unrelated to flying duties, and most unlikely to recur. The policy regarding dizziness, lightheadedness, and vertigo is similar. Health is imperative. Who willingly would fly with a pilot apt to suffer from a seizure or disorientation?

We at the School of Aerospace Medicine (SAM) have long been aware that such cases constitute a fair percentage of our total workload. After all, regulations require syncope cases to be evaluated at SAM before waiver will be considered. Dizziness, vertigo, and related symptoms are so commonly of uncertain etiology that most of these cases from throughout the Air Force are also referred for a "final opinion" (after SAM, there is hardly anywhere else to go). The investigators tasked SAM's Clinical Data Repository to determine the actual number of cases seen.

Between Jun 1974 and Dec 1976, 2,499 individuals were evaluated at SAM for a wide variety of reasons. Approximately 2,117 of these had possibly aeromedically significant illnesses, while 382 (West Point Study and laser examinations) were evaluated because they were members of special study groups (rather than referred for suspected illness). Vertigo, dizziness, LOC, or related conditions were noted in 314 cases, or nearly 15% of the individuals with possibly aeromedically significant conditions. In 165 cases (8%), an etiology other than psychological seemed responsible; i.e., vasovagal and micturition syncope, viral labyrinthitis, alternobaric vertigo, etc. But in 149 cases (7%), the etiology was thought to be either psychological or "unknown." Hyperventilation was specifically noted in 19 cases.

Let us summarize: Nearly half (47%) of the cases of LOC, vertigo, dizziness, and related symptoms evaluated at SAM seem the consequences of either emotional factors or of mechanisms we cannot explain. These unexplained conditions result in great losses of trained and experienced aircrew since they invariably are grounded.

This realization led the investigators to design a controlled study to try to identify how psychosocial factors, emotional arousal, and hyperventilation might contribute to cases of nontraumatic loss of consciousness (NTLOC) and dizziness/vertigo seen at SAM. We hoped that more accurate diagnostic criteria could be developed for use with aircrew.

Fainting, dizziness, and vertigo are relatively benign conditions within the civilian population, seldom causing such severe job disability as in performance of aircrew duties. Consequently, even though they are common, these have not drawn extensive attention from scientists. In most medical care facilities, a significant percentage of fearful or anxious patients who seek help in various clinics, believe they have serious cardiovascular, central nervous system, or other diseases; but are found after adequate study to have subtle, undetected hyperventilation (Lazarus, 1). Some of these patients become severely incapacitated, but the emotional factors are missed (even with psychiatric evaluation sometimes!).

Our aircrew are trained in altitude physiology and are taught the effects of hyperventilating, but few realize the process can be so subtle that it goes unrecognized as the cause of symptoms. Often, there is a predisposing factor which throws the patient off course when he tries to explain his symptoms; i.e., his father died of a heart attack so his shortness of breath and strange symptoms must be related, he believes, to his own "coronary artery disease."

The scientific literature offers some idea of the prevalence of syncope in various situations. Callaghan (2) reported that 4.5% of blood donors faint. Lamb (3) mailed anonymous questionnaires to Air Force aircrew, and about 20% of the respondents reported at least one episode of NTLOC. In a review of

89 in-flight incidents of sudden incapacitation over a 6-year period, Raymon (4, 5) reported that 36 had NTLOC. Three were diagnosed as vasovagal syncope or G_z force intolerance.

Engle (6, 7) has described several mechanisms that may eventuate in LOC. Often the faint occurs when an individual is actually fearful or anxious but highly values "control" and "strength"--a need to manifest "bravery" when he does not have his "heart" in it. Sympathetic autonomic arousal occurs along with conscious denial of threat. Eventually, the circumstances become too overbearing; the individual "gives in;" and parasympathetic autonomic arousal develops abtuptly with peripheral vasodilatation and bradycardia, and consequently, reduced cerebral blood flow and syncope. Some individuals are said to have a narcissistic overconcern with bodily harm.

Graham (8) described the faint as a diphasic physiological response to a diphasic psychological state. The first phase is the autonomic nervous system response to anxiety; the second phase is characterized by a sudden relief from anxiety, with decreased sympathetic discharge and vasodilatation.

Some psychological test data are available from the Minnesota Multiphasic Personality Inventory (MMPI). Ruetz (9) found that blood donors with syncope, compared to blood donors without syncope, had significantly higher depression and hypochondriacal scores. Schmidt (10) in a similar study found fainters to be higher on all scales than nonfainters, but still within normal range.

A number of investigators have suggested that NTLOC is a multivariant phenomenon with various mechanisms working synergistically (7, 11, 12, 13, 14). Hyperventilation has been shown to decrease cerebral blood flow by as much as 40% (14). This deficit may contribute to or actually provoke an episode of LOC in combination with other factors, such as orthostatic hypotension, hypoglycemia, micturition or vasovagal influence. Increased respiratory rate and depth is an expected response to fearfulness.

SUMMARY OF METHOD

All cases undergoing USAFSAM evaluation for syncope, dizziness, and vertigo over an 8.5-month period were seen for psychiatric evaluation by one of the two investigators. A standardized set of data was collected on each, including:

1. Clinical interview focusing on the immediate psychiatric history prior to the reference symptoms; past history with special attention to anniversary dates and object losses; and investigation of events immediately preceding and following the episode (physical and psychosocial).
2. Standardized mental status examination.
3. Rating of attitude present during interview.
4. Rating of affect present during interview.
5. Rating of mental defense mechanisms.
6. Rating of character traits.
7. Rating of thought content at time of reference symptoms.
8. Psychometrics, including Cattell's 16 PF, Cornell Index, Revised Willoughby Questionnaire, Fear Inventory.
9. Hyperventilation experience of 60 deep breaths in one minute and a symptoms checklist.

For all syncope patients, the USAF School of Aerospace Medicine workup (in addition to the psychiatric evaluation) includes a complete physical examination with routine specialty examinations in internal medicine, ENT, ophthalmology, neurology, and other specialties as indicated. Laboratory tests include routine chest x-ray, KUB, skull series, a resting ECG, complete blood count, electrolytes, calcium, phosphorous, VDRL, liver function studies, sedimentation rate, serum lipids, and urinalysis. Also performed on each patient are a tilt test, cardiovascular stress testing, a brain scan, and routine and sleep-deprived EEG's.

In addition to the identified study-group patients, a group of control subjects was similarly evaluated. These patients were randomly selected individuals referred to USAFSAM with possibly aeromedically significant disorders, excluding LOC, vertigo, dizziness, and any known psychiatric condition.

RESULTS

A total of 47 study-group and 31 control-group subjects were evaluated. The results presented here will be limited to only 21 subjects (the "study group") who reported, after hyperventilating, that those symptoms were either very similar or identical to their reference symptoms. This includes patients with symptoms of syncope, dizziness, or vertigo. Their findings are compared to the control-group subjects. In no case did medical evaluation provide a clear explanation for the reference symptoms. Neurological exams on all patients were normal.

Background. None of the control subjects reported any in-flight episodes related to their reference symptoms, but 30% of the study group did so. Death of loved ones is a common history from patients with psychogenic hyperventilation and death anxiety, and higher percentages of the study group than the controls (Table I) reported actual and/or threatened object loss, separation from family, and anniversary distress related to such losses in the two months before the episode. However, separation from family was the only item significantly different ($p < .05$). Interestingly, at least one object loss any time during life occurred in 22 (71%) of the controls but in only 10 (48%) of the study group. This difference was not statistically significant and may only be a function of age, since the controls were somewhat older and would have naturally lost more loved ones. Guilt over an extramarital sexual relationship was noted in 5% of the hyperventilators, but in none of the controls.

TABLE I. CONDITION AT ONSET (within 2 months)

	Hyperventilators %	Controls %	p ≤
Actual object loss	38	32	
Threatened object loss	62	42	
Separation from wife/family	48	17	.05
Anniversary date	14	10	
Extramarital relations	5	0	

The job influence seemed considerable (Table II). The study group reported far greater "fearfulness," "frustration," and "desire for change." Controls reported far greater "satisfaction." The average age of the two groups varied, with controls being older (35.6 vs. 28.5 years, $p < .01$). The rank distribution was skewed significantly toward higher ranks for controls ($p < .05$). The apparent lack of success with promotion and the sense of job frustration, fearfulness, desire for change, and degree of job stress seem possibly related.

TABLE II. FEELING ABOUT JOB AT TIME OF EPISODE

	Hyperventilators %	Controls %	p ≤
Resentful	24	10	
Fearful	38	4	.01
Frustrated	57	16	.01
Desired change	43	6	.01
Satisfied	57	94	.01
Neutral	14	23	

Subjects were rated for job stress on a scale from 1 (none) to 5 (severe). None of the controls were rated 5 (severe for stress) and only 16% were rated 4 (much). The study group ratings were 24% and 19%, respectively.

Similar determinations were made for stress secondary to relationships with wife, children, and parents. There were no apparent differences for wife and children, but 27% of the study group, compared to only 8% of the controls, were rated high (3, 4, or 5) for stress regarding their parents. Each subject was asked to rank on a scale from 1 (not present) to 5 (very strong, almost out of control) their affect at time of onset of the episode, including anger, resentment, depression, fear, helplessness, anxiety, elation, frustration, and worry. The study group appeared from the results to have been slightly more "depressed" than the control group ($p < .05$). There was an overall emotional arousal apparent in the study group with many more (than controls) reporting emotions that were 4 (very intense), or 5 (very strong, almost out of control). The presence of helplessness and worry was significantly discriminating ($p < .05$). The study group reported a greater loss of self-esteem ($p < .10$), with 33% reporting "reduced a great deal" compared to 6% of the controls.

There was a family history of fainting in 16% of the study group and 7% of the controls. Presyncopal symptoms were reported by 43% of the study group and 13% of the controls ($p < .05$). Two or more episodes of symptoms had occurred in 33% of the study group and 7% of the controls. In each group, 10% reported previous psychiatric experiences.

Events Immediately Before Onset. A nearly equal number of each group, 43% of study group and 45% of controls, had an antecedent physical illness; and 24% and 33%, respectively, had had a medical procedure of some kind (Table III). While 43% of the study group felt unable to act, only 7% of the controls perceived this ($p < .01$). Significantly more of the study group (14%) than the controls (none) experienced pain ($p < .05$). Vegetative symptoms within a week of the episode are presented in Table IV. These could be explained by the antecedent illnesses reported.

TABLE III. IMMEDIATE EVENTS BEFORE ONSET

	Hyperventilators %	Controls %	p ≤
Antecedent physical illness	43	45	
Medical procedure	24	33	
Pain	14	0	.05
Sight of blood, injury, mutilation	19	7	
Fantasy of mutilation	24	7	.10
Perceived inability to act	43	7	.01
Prolonged recumbency	10	0	.10
Prior alcohol use	5	0	
Prior drug use	10	0	.10

TABLE IV. VEGETATIVE SYMPTOMS IN WEEK PRIOR TO EPISODE

	Hyperventilators %	Controls %	p ≤
Sleep restless	24	16	
Early A.M. awakening	5	19	
Trouble falling asleep	19	10	
Nightmares	0	0	
Appetite decreased	19	3	.10
Diarrhea	5	0	
Nausea/vomiting	19	0	.05

Immediate Consequences and Events. Since the control subjects did not experience an acute episode of LOC, vertigo, or dizziness, no comparison was attempted between groups for immediate consequences. The results of investigations into the psychological and physical consequences are presented in Tables V and VI, respectively. Most noteworthy, 43% of the study-group patients had thoughts that they were seriously ill following the symptom episode, and 71% seemed to have factors of secondary gain.

Of the 18 study-group patients who had loss of consciousness, 10% suffered trauma on falling, 10% were incontinent of urine, and 5% of feces. These findings are generally believed to be indicative of seizure disorders and atypical of "simple" syncope. Since none of these patients were found to have seizure disorders, it seems these symptoms also can occur occasionally in (nonepileptic) syncope.

TABLE V. IMMEDIATE PSYCHOLOGICAL CONSEQUENCES AND EVENTS

	Hyperventilators %	Controls %
Dreams	0	0
Thoughts of severe illness	43	0
Thoughts of insanity	6	0
Thoughts of death	19	0
Secondary gain	71	0

TABLE VI. IMMEDIATE PHYSICAL CONSEQUENCES AND EVENTS

	Hyperventilators %	Controls %
Seizure activity	0	0
Trauma on falling	10	0
Urinary incontinence	10	0
Fecal incontinence	5	0

Standardized Mental Status Examination. Only three of 19 attitudes, rated on a scale of 1 to 5 (least to most), discriminated significantly between groups. The study group appeared more "dependent" ($p < .05$), more fearful ($p < .05$), and considerably more ingratiating ($p < .01$). Similar ratings of 13 affects revealed no significant differences. There was a trend for the hyperventilation group to be rated as feeling more guilty. The controls were more often that the study group thought to have "appropriate" affect ($p < .10$).

Three of 14 "mental defense mechanisms" rated differentiated the groups: Projection ($p < .001$), intellectualization ($p < .01$), and repression ($p < .05$), with the study group thought to use these more than controls. Seven of 34 "character traits" were significantly different: suspicious ($p < .05$), evasive-guarded ($p < .01$), meticulous ($p < .01$), perfectionistic ($p < .01$), indecisive ($p < .05$), naive ($p < .001$), and introverted ($p < .001$), all descriptive of the study group and not controls.

One set of variables, related to thought content, was surprising to the investigators: only two of 23 rated items discriminated between groups. The hyperventilators were far more "indecisive" ($p < .05$) and "isolated" ($p < .01$) than controls. Many items which we expected to characterize the study group were characteristic of both groups; i.e., preoccupation with loss, death, loss of control, helplessness, and phobias (actually 15% of hyperventilators had either "slight" or "mild" phobias while the controls had none, but this was not significantly different ($p < .10$). Three items were not characteristic of either group: suicidal ideation, ideas of reference, and bizarre thoughts.

Hyperventilation Symptoms. Table VII shows the results for both groups resulting from 1-minute of heavy breathing at the rate of one breath per second. Six of 17 items were significantly different, with the study group showing the symptom more commonly than the control group. Most impressive, the hyperventilation group very commonly reported three symptoms--tingling of the hands and feet, dizziness, and lightheadedness (more than 86% for each); but only 81% of the controls reported lightheadedness, and much less frequently reported the other two symptoms. Chest pain, which is a relatively common symptom of the psychogenic hyperventilation and death anxiety syndrome, was not typical for either group. Syncopal/presyncopal symptoms were reported by 52% of the hyperventilation group and none of the controls. Spontaneously, three patients who had been referred to SAM for evaluation of "vertigo" or "dizziness," and five patients referred for syncope, reported the symptoms of hyperventilation were "the same" as the symptoms of their illness. The remaining 13 study-group patients, when questioned about similarities, reported the symptoms were "very similar" or "the same."

TABLE VII

Symptoms	Hyperventilators %	Controls %	$p <$
Tingling of hands and/or feet	95	65	.01
"Thickheaded"	43	35	
Disoriented	24	10	
Unable to think clearly	38	13	.05
Dizziness	86	52	.05
Lightheaded	95	81	
Pains in chest	0	3	
Queasy	19	10	
Nauseated	24	6	
Weakness in arms or legs	48	13	.01
Blurred vision	48	19	.05
Tunnel vision	29	16	
Faint	38	16	.10
Objects seem smaller	10	0	.10
Sounds seem distant	14	19	
Feel apart from reality (spaced out)	40	13	.05
Headache	14	10	

Psychometrics. The Cornell Index study-group average total score was 4.8 and for controls only 1.1. Both of these scores were well below the cutoff (between 8 and 9) which reliably screens 75% of individuals with mental health problems for selection for flying training. Yet, this difference was highly significant ($p < .001$).

No significant differences are apparent, comparing the performance of each group on the Revised Willoughby Questionnaire and Fear Inventories.

Cattell's 16 PF has three scales that seem to differentiate these two groups (at $p < .05$ or better): H, N, and Q_3.

DISCUSSION

Vertigo, dizziness, and loss of consciousness are symptoms responsible for USAFSAM referral in nearly 15% of the cases. Nearly half of the time, we are unable, after thorough evaluation, to explain their cause.

The purpose of this study has been to define the psychosocial factors involved in these cases. We hoped to find constant differences that would permit formulation of a "typical profile" of the different subgroups to expedite diagnosis and disposition of such cases.

In another paper (publication pending), we focused on that group of patients with syncope and compared them to controls. There is a significant overlap between the syncope group and the group of hyperventilators, the subjects of this study. Of the 34 patients we studied with syncope, 18 were found or suspected to hyperventilate as part of their pathophysiology. The final diagnoses of these 34 cases also reveal overlap of the groups. Vasovagal (68%) and micturition (12%) syncope were the most common diagnoses. One case each was attributed to an associated illness and G-force intolerance. The etiology remained unknown in five cases (15%), which is much better than we expected based on the experience for the 2.5 years preceding this study.

Our findings add credibility to the hypothesis that fainting is a multivariant phenomenon with several factors often working synergistically. We were somewhat surprised to find that exploration of "thought content" did not reveal major differences. Because of our experience and the literature, we thought the study group would manifest more concern for control, death and dying, object loss, helplessness, and phobias. We do know from clinical experience that emotionally ill hyperventilators at first strongly deny these concerns, even though present, and it is possible that the investigators simply missed these concerns in their brief contact with the patients. Alternate explanations for not finding the expected differences include the unlikely assumption that these data are not relevant to these cases; or more likely, the data do not differentiate because they apply significantly to both groups. Inspection of the raw data confirms the latter. Any illness may represent a great threat to an aviator, especially if he is a strongly achievement-oriented person, and may influence him to worry about loss of control and to feel helpless.

The results of the Cornell Index reveal, we think, how really healthy aviators seem. The average total score for controls was 1.1, and for the study group, 4.8. Both of these groups were composed of individuals who supposedly were "ill," but both had scores far below the cutoff point (between 8 and 9), which identifies 75% of individuals with significant emotional problems. Even so, this slight difference was highly discriminatory. Often flyers may wish to seem more healthy than they actually are because their careers are in the balance.

CONCLUSION

The development of "typical profiles" must await future publications resulting from this study; we have not finished analyzing the data for each subgroup, but we expect to finish soon. A general description of features that seems to differentiate patients with loss of consciousness, dizziness, or vertigo and hyperventilation from other patients is possible. They are often separated from their family and have prominent job maladjustment. Parental conflict is common. They tend to be affectively aroused, especially feeling worried and helpless; self-esteem may be low; and as a group, they show signs of dependency, obsequiousness, and fearfulness. Prominent mental defense mechanisms include projection, intellectualization, and repression; they seem to be suspicious, evasive, guarded, meticulous, perfectionistic, indecisive, naive, and introverted. They react to hyperventilation demonstration with a larger amount and greater variety of symptoms, especially paresthesias, dizziness, and lightheadedness.

A score of 5 or higher on the Cornell Index is apt to be significant. Other psychometric description must await further analysis.

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DISCUSSION

Fitzgibbon: Were the electroencephalograms of these patients always normal? Did you find any particular differences in that strong and surprisingly large subgroup of patients who had fecal and urinary incontinence?

Boydstun: The first question is related to the electroencephalograms on these people. All of them had extensive complete physical and neurological evaluations and EEG's. There was no neurological or electroencephalographic abnormality noted in any of the study groups. Interestingly enough, there were a few of the subjects who after hyperventilating for five minutes for the EEG, came to the psychiatric interview already having discovered the cause of their symptoms. When they were asked to hyerventilate again as a part of the study they would say for instance, "Well I have already done that in the EEG. I know what it does. It causes my symptoms." Now as to the second question that Dr. Fitzgibbon asked, I must admit there is disagreement between the two authors of this paper. I have always felt that this sign usually is a symptom seen in seizure disorders and carries a poor prognosis. Dr. Sledge feels that this is simply a sign of a disruptive central nervous system event and is not necessarily a prognostic sign or correlated with a seizure disorder. I personally was surprised to find that 10% of the syncope group was incontinent of urine and I was even more surprised to find that 5% were incontinent of feces.

Triebwasser: Were there any EEG differences between those who did not experience urinary incontinence versus those who did.

Boydstun: There EEG's were all interpreted as normal.

O'Connor: I have a number of questions concerning this very interesting paper. I am very relieved to see that other people have this incidence of incontinence, even of feces, of which I must say always worrys me. Do you control the tidal volume during hyperventilation? We try to use a standard bag and make them empty it with each breathe. I am surprised at no seizures because we know in conditions like Stokes-Adams syndrome where there is a catastrophic drop of blood pressure, we find seizures of the tonic/clonic variety. Did you not see occasional twitching of the fingers or mild tonic movement? Did you find any distinctive or identifiable difference in the EEG during hyperventilation in those who you regard as suffering from the hyperventilationary syndrome?

Boydstun: The way I do the hyperventilation experience is to show the patients how deep to breath (that is, as deep as they can) at one breathe per second for 60 breathes in a minute's time. We have no evidence that there is any difference in the electroencephalogram in those who hyperventilate from those who were not apparently hyperventilating. We haven't done a close analysis of the EEG's but there were no gross abnormalities noted that would differentiate those two groups. The patients that come to us, have recorded histories. Unfortunately, we very seldom witness a syncopal episode. Some do in fact faint during venipunctures when they first come to the Consultation Service. But, of the ones we saw for this particular study, the 18 patients that fainted and who also were found to hyperventilate, there were no reports that accompanied the patient suggesting they had tonic/clonic movements. We commonly do have such reports in other syncopal patients that are referred to us. This is often the case, especially if their well meaning friends sit them up prematurely before they regain consciousness.

Clement: Did you try to combine your tables in order to see if the distinction between your control group and the others becomes more clear? Such a combination would be very useful for the base flight surgeon. If he has a pilot who has family problems, who feels frustrated and perceives an inability to act, your tables suggest he should provisionally ground this pilot.

Boydstun: Those are interesting observations. Yes I think it would be worthwhile to describe the typical profile and make this available to flight surgeons. Perhaps we will be able to do that shortly.

β-adrenoceptor Antagonists - Central Effects

by

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β-adrenoceptor antagonists are used widely in therapeutics, and though they were intended for the treatment of angina pectoris and cardiac arrythmias, it is their ability to lower blood pressure in hypertension that has proved to be the major clinical application. These drugs have aroused interest in aviation medicine because of their possible use in the management of mild hypertension, but the question arises whether their use in aircrew may be accompanied by unacceptable changes in the function of the central nervous system. There is evidence that their hypotensive effect may involve cerebral mechanisms, and that their use may lead to behavioural disturbances such as dreams and visual hallucinations. They may be used in the management of neurological disorders such as essential tremor, thyrotoxicosis, anxiety, migrane and possibly schizophrenia, and it is these observations which suggest that a cautious approach may be appropriate when impaired central nervous activity is to be avoided.

The concept of using β-adrenoceptor antagonists in angina pectoris and myocardial infarction to protect the myocardium from sympathetic drive was pioneered at the research laboratories of Imperial Chemical Industries, Alderley Park, United Kingdom. From the early studies with pronethalol and propranolol many compounds have emerged with varying properties, though it would appear that efficacy is related to the cardiac β-blocking activity of each compound. It is the variety of compounds available which suggests the possibility that appropriate choice may minimise any central effects, and so provide a drug which would be acceptable to individuals, such as aircrew, who carry out highly skilled work.

Essentially, the compounds are antagonists, though some also have agonist activity. In the latter case they have affinity for the receptor, but also possess some intrinsic activity in their own right. The antagonists are used to overcome the effect of stimulation of the cardiac β-receptors, but as stimulation of the vascular and bronchial smooth muscle receptors leads to relaxation, blockade of these receptors may allow unopposed α-receptor activity to predominate with peripheral vasoconstriction and bronchospasm. It is for this reason that effort has been directed to the development of antagonists with cardiac receptor selectivity, as cardio-selectivity may be important in the management of hypertension in patients with asthma.

There are other properties of the β-adrenoceptor antagonists which vary between the compounds available. The agonist or Intrinsic Sympathometic Activity (ISA) which may be pronounced is not fully understood, though excessive agonist activty would be contra-indicated. However, partial agonist activity may be useful, as it may minimise the undesirable effects of peripheral blockade. Some drugs also possess a Membrane Stabilising Action (MSA) which is a local anaesthetic or cardiac depressant effect, but this property is considered to be of little importance in current therapeutics, at least as far as the management of hypertension is concerned. Other properties are duration of action and potency. There is considerable interest in the use of longer acting drugs for "once a day" therapy, and it may be that a molecule which has a high potency as a β-receptor antagonist may possess less side effects of a non-specific nature.

Several mechanisms may contribute to the effect of these antagonists, including a decrease in plasma renin activity and in cardiac output. However, the hypotensive effect is related to a reduced peripheral vascular resistance, and as the peripheral vasodilatory vascular receptors are blocked by these antagonists, this mechanism cannot be the basis for the hypotensive action of these drugs. It is in this context that blockade of β-receptors within the central nervous system has been suggested with reduced sympathetic nervous tone. Indeed, there is evidence that antagonists may lower blood pressure when injected into the cerebral ventricles, but such a mechanism may not apply to all β-antagonists, and the effect may not be specific to β-adrenoceptor activity.

The central hypotensive activity of the isomers of propranolol has been studied by several workers. In anaesthetised cats intraventricular administration of d- and d-l propranolol produces a hypotensive response, and so it has been suggested that there is a central component in the response to propranolol, and that it may be independent of β-adrenergic blocking activity, at least, as it is understood in the peripheral vascular system. In similar doses only the d-l isomer possesses cardiovascular β-receptor antagonism. However, the suggestion that the central effect of d-l propranolol may not be related to its β-adrenoceptor antagonism, is not supported by studies in conscious animals. In conscious animals the hypotensive effect seen with d-l propranolol on intraventricular injection is not seen with the d-isomer. It would appear that central mechanisms may be involved in the hypotensive action of propranolol, and it is likely that such a mechanism may involve diminished sympathetic nervous activity, but the role of β-receptor blockade in this mechanism is uncertain.

The systemic administration of β-adrenoceptor antagonists in man not only modifies the cardiovascular system, but also leads to psychological, neurological and behavioural effects. Patients complain of lack of concentration, dreams, and on occasion, visual hallucinations. The agents are also useful in disorders of the nervous system which modify affective behaviour. There is ample evidence that central adrenergic mechanisms are involved in affective behaviour, reward and learning, and in the regulation of muscular tonus and activity, and there is also evidence that similar mechanisms may be involved in the control of vigilance, and in sleep and wakefulness. Some, if not all, β-adrenoceptor antagonists penetrate the brain, and so may induce central effects by the β-blocking activity through β-adrenergic mechanisms, or by non-specific activity.

The drugs may also have an action outside the blood brain barrier. Clinical studies on anxiety suggest that the usefulness of β-adrenoceptor antagonists is not due to their possible central activity, but is related to the relief of somatic symptoms. In this way they be ineffective in the management of anxiety of a central or psychic nature. d-l propranolol, but not its relatively inactive isomer d-propranolol, is effective in the management of anxiety, while practolol which does not cross the blood brain barrier to the extent of propranolol would appear to have the same effect in anxiety as d-l propranolol.

On the other hand studies in animals add difficulties to the somewhat straight forward interpretation of the effects of these antagonists on the central nervous system as indicated by the control of the peripheral manifestations of neurological and psychological disorders. Modulation of behaviour may be brought about by both the d-l and d-isomer of propranolol, and would suggest that these effects, which are likely to be central in origin, may not be related to the receptor blocking activity of the compound. It is difficult to be certain at present of the significance of these findings to man, as the doses used in animals are frequently high, but the possibility arises that the differential effects of d- and d-l propranolol on the cardiovascular and nervous systems seen peripherally in man may not hold centrally. Many of the effects of d-l propranolol may be due to its specific β-receptor antagonism, but, it cannot be excluded at present, that the effects on behaviour may be non-specific.

There can be little doubt that, at least, some of the compounds used as β-adrenoceptor antagonists have central effects which modify the cardiovascular or nervous system. The effect of these drugs on the central nervous system suggest that perhaps the use of β-adrenoceptor antagonists may lead to modification of human performance. Only a few studies have been carried out, and these have been concerned mainly with propranolol. There is some conflict in the results, but overall no consistent evidence of an effect on performance with doses of propranolol up to 120 mg within a few hours of ingestion have been observed. Similarly, studies on the electroencephalogram within 3h of ingestion, and on the contingent negative variation within 80 minutes of ingestion, have failed to reveal any effects. However, in a recent study changes in the electroencephalogram were observed from 4-6h after ingestion of 160 mg propranolol. Impaired behaviour with propranolol may be delayed beyond the period of time which has been used for most studies involving the assessment of performance, and it is possible that, if there are effects on performance in man, they may be of a subtle nature. A more sophisticated approach to the effects of these drugs on the central nervous system is indicated, and these studies should include both time and dose response observations.

DISCUSSION

Kelly: I would like to ask one of the speakers, in practical terms, if we are to put our aircrew on any of these drugs what sort of checks should we do on them before we allow them to go back to flying?

Cooke: I can tell you what is going on in other countries at the moment. In New Zealand they are allowing the use of beta-blocking drugs as a hypotensive in commercial airline pilots. There they demand a period of three months from the institution of the drug to firstly assess what's its final hypotensive effect may be, and secondly to get a stabilization of the dosage. Like all other hypotensives, the trouble with using propranolol or one of the other beta-blockers is that you may start with one dose which seems to cause no side effects, and then have to increase the dose to get good control. And so in New Zealand they suggest a period of three month period of observation. I think it is being used in Holland, among commercial airline pilots. In England, I think we have had five or six commerical airline pilots flying on it. Each one of these has gone through a prolonged grounding plus a period with checks on simulators and flight checks before returning to duty. None of these pilots is flying in a solo pilot operation. As far as doses are concerned, I think there is the clear cut recognition that a lot of the side effects are dose related and the general attitude is to keep the dose as low as possible. In this country so far I think, the maximum dose allowed is around 80 mg in a single dose.

Nicholson: I won't answer this on the clinical side of it, but what little information is available, I think it is possible at the moment to select a beta-blocker which is on current information least likely to cause harm. I think that perhaps more attention could be paid at the moment to the use of other beta-blockers which based on pharmacological grounds, may be more suitable and practical. We have nine beta-blockers in this country to choose from, and on many counts propranolol should be at the bottom of the list.

O'Connor: I would like to ask Professor Cooke the answer to this dilemma. Our psychiatrists were not allowed to use psychotropic drugs in practicing aircrew. We know that there is often a psychological or psychosomatic impairment in hypertension. Many people will tell you that by using relaxation therapy, you can get some of their blood pressures down. Do you know when they are using beta-blockers to control hypertension, whether we are dealing with the beta-blocking effect or the psychotropic effect?

Cooke: I think it can be said that small doses of beta-blockers, those which are unlikely to have much behavioral effect, do exert very considerable peripheral effect and in particular, they will block the peripheral manifestations of anxiety. Now, this certainly is a strange sensation which if you haven't tried, you might find interesting in that you can be put under stress, such as standing here, without any rise in pulse rate, without any shake of the microphone, and without any sweating. That is an effect which will undoubtedly in anxiety prone individuals, be associated with a fall in the pulse rate beyond that expected from beta-blockade, and probably a fall in the blood pressure as well. But, I don't think it is the same as the effect you see from large doses which are commonly given by psychiatrists for diseases associated with anxiety prone manifestations, schizophrenia, and so on. In this small dose situation, I think that is a peripheral effect.

Nicholson: There has been a lot of work done on these beta-blockers in anxiety, and some psychiatrists differentiate anxiety of somatic symptoms from that of purely psychic origin. I don't know whether you do or not; but, some investigators have pointed out that these drugs are only useful in anxiety when there are somatic symptoms. They are not of any use in an entirely psychic or central origin.

Fuchs: I would like to bring this entire program back to a very central point. Since it's the Air Forces' mission to fly it is obvious the aeromedical specialists and practioners must assist the fliers do their best. I refer to Professor Cooke's first remarks and slides and I remember he pointed out an elevated blood pressure has influence for the prognosis of the individual, but obviously not for the physical fitness for flying. When considering this point and keeping in mind the restrictions as outlined by Wing Cmdr Nicholson, we should consider whether our papers as set in the past 20, 30 years for elevated blood pressure, are really relevent for the operation of the fliers. We know well from the 1,000 aviators study by the United States Navy as well as from the similar studies done in other Air Forces, that the standards both for systolic and diastolic pressure have changed remarkedly. So, my question as a result of these discussions is, do we really need new tables of so called normal blood pressure, as a measuring stick for using any therapy or medication?

Cooke: I think we shall have to wait really to see how the British and other worldwide studies on the treatment of mild degrees of hypertension come out. I think that they could very materially effect our whole attitude to the use of drugs in blood pressure.

Dietz: Dr. Cooke, please clarify your remark that the cardiac output is significantly decreased under stress because of the negative chronotropic and ionotropic effect of the drug. Do you mean beta-blockers will decrease the physical working capacity also in relatively healthy, asymptomatic persons?

Cooke: There have been many studies as you well know, which show when an individual is "beta-blocked" he loses a certain proportion of his physical work capacity. Whether you wish to measure this on a treadmill or on any other stress test, you can show that he can no longer complete the same degree of exercise task that he was previously capable of. I see no way of getting around this. It would mean that in the military aviation context, if a pilot or member of the crew was "beta-blocked" as far as escape or severe physical activity was concerned, he would be under a limitation.

THE PREDICTION OF THE EXISTENCE OR NONEXISTENCE OF CORONARY ARTERY DISEASE USING ROUTINE CLINICAL LABORATORY MEASUREMENTS

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SUMMARY

We have previously reported an association between angiographically proven coronary artery disease (CAD) and elevated levels of serum cortisol (1). Multivariate analysis has shown that plasma cortisol contributes significantly over and above cholesterol and age as a discriminator between those patients with positive coronary arteriograms and patients with negative studies. We used data from 57 patients to develop a multiple logistic risk function for cholesterol, age, and plasma cortisol. The resulting predictive model demonstrated a predictive value of 86% for a positive test and predictive value of 89% for a negative test. This model was then tested on 78 additional patients who had coronary angiography. The predictive value of a positive test was 91% and the predictive value of a negative test was 78% on the validation group. If further testing continues to validate these findings, it appears that plasma cortisol may be a new risk factor for the prediction of CAD.

INTRODUCTION

In a previous publication we found an association between elevated levels of plasma cortisol and moderate to severe coronary artery disease (CAD) as diagnosed by coronary angiography (1). Using multivariate analysis, we found that plasma cortisol contributes significantly over and above cholesterol and age to the prediction of positive coronary angiography. In the present study we have developed a multiple logistic risk function that uses these three measures to predict the probability of CAD.

METHODS

Serum cholesterol, 0930 hr plasma cortisol, and age were measured in an initial group of 57 patients. These patients were apparently healthy asymptomatic USAF aircrew members referred to the USAF School of Aerospace Medicine (USAFSAM) Consultation Service for a medical evaluation because of abnormalities detected on their annual medical evaluation. These patients underwent cardiac catheterization because of an abnormal ECG response to treadmill stress testing, an acquired bundle branch block, or isolated episodes of a supraventricular tachyarrhythmia.

From these data, coefficients for the multiple logistic risk function were estimated for the 0930 hr plasma cortisol and for the product of serum cholesterol and age. The product of cholesterol and age was used since it was the best single predictor of CAD in our sample. The probability, then, of having moderate to severe CAD is estimated as:

$$P(D) = \frac{1}{1+e^{k}}$$

where: $k = 9.8202 - 0.00066639 \times (\text{chol} \times \text{age}) - 0.18473 \times (\text{0930 hr plasma cortisol}) + \ln \frac{1-P}{P}$

p = prevalence of CAD

Based on a 40% prevalence of CAD in USAFSAM cardiac catheterization patients, those patients with an estimated probability of CAD of .4 or greater were classified as diseased. The actual presence or absence of CAD was verified by coronary angiography in all cases.

The model was then tested on a validation set of 78 additional USAFSAM cardiac catheterization patients.

RESULTS

In the initial group, the prediction model correctly identified 83% of the patients with moderate to severe coronary artery disease (sensitivity) and 91% of the patients without disease (specificity). The predictive value of a positive test (Prob $\geq$ .4) was 86% and the predictive value of a negative test (Prob $<$ .4) was 89% (see Table I). In the validation group, the formula correctly identified 40% of the patients with moderate to severe disease (sensitivity) and 98% of the patients without significant disease (specificity). The predictive value of a positive test was 91% and the predictive value of a negative test was 78% (see Table II).

The mean age, cholesterol, and plasma cortisol of the initial group were, in most cases, higher than for the validation group (see Table III).

DISCUSSION

With the addition of plasma cortisol to the established risk factors of age and cholesterol, we have developed a predictive formula which has a high predictive value for CAD. These data suggest that cortisol may be a new risk factor for CAD. This high predictive ability is validated by the use of cardiac angiography as a definitive endpoint for CAD. Other studies involving CAD have relied on noninvasive cardiac diagnostic procedures or autopsy data.

In our validation group the sensitivity decreased compared to the initial group. One possible explanation for this decrease is the decreased levels of serum cholesterol, plasma cortisol and the lower age of the validation patient group with positive coronary angiography. At this time no explanation for this risk factor decrease is readily apparent other than possible effects of an increasing awareness within our population of cardiac health.

Although this model has a high predictive value in the USAFSAM cardiac catheterization population, extrapolation of these results to other populations may not be valid. Further testing of this model to determine the contribution of cortisol as a risk factor, and comparisons to other predictive models for CAD (such as the Framingham model) will be performed.

TABLE I
Initial Group Classification Results

	Coronary Angiography +	Coronary Angiography -	
Prob of CAD $\geq$ .4	19	3	22
Prob of CAD < .4	4	31	35
	23	34	57

Sensitivity = $\frac{19}{23}$ x 100 = 83%

Specificity = $\frac{31}{34}$ x 100 = 91%

Predictive value (+) = $\frac{19}{22}$ x 100 = +86%

Predictive value (-) = $\frac{31}{35}$ x 100 = 89%

TABLE II
Validation Group Classification Results

	Coronary Angiography +	Coronary Angiography -	
Prob of CAD $\geq$ .4	10	1	11
Prob of CAD < .4	15	52	67
	25	53	

Sensitivity = $\frac{10}{25}$ x 100 = 40%

Specificity = $\frac{52}{53}$ x 100 = 98%

Predictive value (+) = $\frac{10}{11}$ x 100 = 91%

Predictive value (-) = $\frac{52}{67}$ x 100 = 78%

TABLE III

Means

	Coronary angiography	N	Cholesterol	Age	0930 hr plasma cortisol
Initial Group	+	23	276.2	46.3	13.66
	-	34	223.7	39.7	9.60
Validation Group	+	25	241.2	44.4	11.13
	-	53	209.0	39.9	9.20

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DISCUSSION

Fitzgibbon: It is a great pleasure indeed, to have somebody prick the cholesterol bubbles, and to point out that in actual fact there is a tremendous biological variability in cholesterol. Many years ago, 16 odd years ago, I started doing blood cholesterol in couplets on all patients admitted to the hospital. These were obtained fasting, lying in bed on three successive mornings. I learned, very soon of course, as others have that if you have the patient get up and about and do the blood cholesterol after being up half an hour, you can raise the blood cholesterol by approximately 12%. This is a mean value. On the successive days we were horrified to find changes of up to 100 mg%. This set Dr. John Nixson, our clinical chemist, and myself in a chase across Canada, quering by mail the members of the Cardiovascular Society and the Canadian Association of Clinical Chemists. I was pleased and a little surprised to note how very few of my cardiological colleagues paid very much attention to isolated cholesterol estimations. Dr. Nixson was equally pleased and equally surprised how very few of his clinical chemist colleagues felt their methodology for measuring cholesterol in the lab was any good. Unless you go back to the old Abel-Kendall method of doing blood cholesterol estimations, most of the newer autoanalyzer methods are afoot with problems and failure of reproducibility. One of the difficulties in using predictive values that a blood cholesterol measurement may not actually be a truely representative value Perhaps we tend to pay too much attention to changes of 8, 10, or 11 milligrams in blood choesterol estimations which may be of no importance. The variations in triglyceride estimations, if you start doing these in triplicate on your patients, are even more gross. As a matter of fact our laboratory after three months of doing this asked me to stop doing them because we were really wasting the laboratory's time and we had proved our point over and over again. I would like to ask Dr. Troxler a question along the same lines. What is the reproducibility of your 0930 plasma cortisol measurement in the patients that you studied? How did you approach this problem? How many have you done and what is the reproducibility of this isolated measurement?

Troxler: The reproducibility of the 0930 cortisol unfortunately was not on the slides and I do not have the actual values here with me. I can tell you the standard error of the mean of the values for those having no disease and minimal disease do overlap. The standard error of the mean of the values for those having significant disease do not overlap with the former. Now as to your comments concerning the problems with blood cholesterol, our coefficient of variation for this measurement on the average is 2.0%, which is acceptable in most laboratories.

Cooke: Like everybody who has worked with steroid metabolism in the past, I don't think I can let it go without noting that, any plasma cortisol estimation, at whatever time of day, can be effected by all sorts of factors including the stress of actually having the venipuncture done. I recall we used to put in venous cannulae and leave them in for 12 to 24 hours before we would accept that that particular aspect had not been effecting the actual cortisol value. Nevertheless, it strikes me that it could be the response to stress of this kind, in itself, that might be one of the predictive factors that you are looking at.

Troxler: We agree with that. We think we actually are giving these patients stress because of the threat of loosing their job resulting from an evaluation at our institution. Perhaps we are actually testing the response of the adrenal gland to this stress. In the paper we reported and referenced in the preprint, we made this point quite clear and emphasized that this study may not be reproducible in other populations, especially those conducted in civilian institutions. However, I think that anyone at an aeromedical evaluation center has the same opportunity we have to test this response because of the treat of job loss.

Zumoff: I want to make a comment and ask a question. Some years ago we had the occasion to do daily cholesterol measurements over periods of time, sometimes months in a variety of patients within metabolic ward conditions, resting, and on a fairly stable diet. We used a very good method, much better than the current auto-analyzer methods. We did Schoenheimer-Sperry determinations using digitonin precipitation which is as good a method as there is, and we consistently found the coefficient of variation to be approximately 20 to 25% in almost all of our patients. This means that at an average level of 250 mg%, a fluctuation of plus or minus 125 mg% would be considered within the normal range. A number of observers during this conference have suggested that the incidence of a positive stress test is too great for one to use this as a basis for grounding flying personnel. Others have disagreed, but many have expressed that opinion. There was a fairly general agreement that the presence of a definitely positive angiogram would be sufficient. How close are we on the basis of these and similar studies to a noninvasive approach of predicting the results of this invasive procedure, so that it would be reasonable to ground people without necessarily doing the actual angiogram?

Troxler: I think that before we advance to that stage we have to have at least two or three independent noninvasive tests to predict probability of a positive angiogram. In our experience, and I'm sure every one else's experience too, when we use the panel approach (e.g. liver function battery), if only one test is abnormal we tend to ignore its significance or assume the laboratory made a mistake. But if we have say three or four abnormal tests all supporting dysfunction of a given organ or system, we are willing to make a diagnosis and a statement regarding prognosis. So I think we will be able to use the same rational in evaluating our aircrewmembers for coronary disease. If we have three noninvasive tests having reasonable sensitivity, and predictive value, we may be able to make reasonable aeromedical decisions without resorting to coronary arteriography. Unfortunately we are not at that point at this time.

Kelly: I would like to comment on that last question and point out that at the tail end of my paper, I did mention the possibility of improving the specificity of the stress exercise test by using a beta-blocker, 80 mg of oxprenolol. It does seem in our small studies so far, that the specificity can be brought more nearly to 100% for the exercise test in that those with coronary artery disease still had a positive test after receiving the drug, whereas, those in whom angiographically it had been shown that coronary artery disease was not present, did not have a positive test after 80 mg of oxprenolol.

Fitzgibbon: I have a historical reminder which takes into account the beta-blockers and their central nervous effects. I'm sure we all remember that in the early days of the two-step test, Dr. Master used ergot alkaloids which also had some rather strange central nervous system effects. He used this for a while in an attempt to demonstrate that the two-step test would be more specific and I think with some success.

COMPARISON OF PLASMA AND URINARY STEROIDS IN MEN WITH TYPE A AND TYPE B BEHAVIOR PATTERNS

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Summary

A large number of urinary and plasma steroidal parameters have been compared in men with Type A and Type B behavior patterns. Two differences were found between these groups: (1) Type A men showed higher daytime (0900-1800) urinary excretion of testosterone glucuronide than Type B men (24 μg vs 15 μg, $P < .05$); (2) Type B men showed higher average plasma concentrations of dihydrotestosterone (93 ng/dl vs 79 ng/dl, $P < .05$). The results of this study suggest that it may be possible to decrease the risk of coronary heart disease in Type A men by intervening to change the levels or antagonize the effects of certain steroid hormones.

Introduction

Some years ago, two of us described two distinctive behavioral patterns in adults, Type A, comprising intense competitiveness and an enhanced sense of time urgency, and Type B, featuring relative placidity and acceptance of the course of events, without domination by clock and calendar, and reported that the incidence of coronary heart disease (CHD) was many times greater in Type A individuals (1). The latter observation has since been confirmed by others (2). It was realized from the start that a difference in CHD incidence between Type A and Type B individuals implied a difference in one or more mediating physiological or biochemical factors. A continuing effort has been made to define such factors, with the result that Type A individuals have been found to excrete more norepinephrine in the urine (3) and to have less adrenocortical responsiveness to ACTH stimulation (4) than Type B individuals. Reports by others (5-9) concerning abnormalities of steroid excretion in CHD patients, and the preeminent epidemiological fact that there is a profound sex difference in the incidence of CHD (10, have focused attention on steroidal risk factors for CHD and prompted us to carry out a comprehensive investigation of possible differences in plasma and/or urinary steroid levels between Type A and Type B individuals. Preliminary results of this investigation are reported in this communication.

Subjects and Procedures

Selection of subjects

Normal healthy male volunteers, aged 32-66, were interviewed in San Francisco by one of us (M.F.) and categorized as Type A or Type B according to previously published criteria (1). They were then divided into three series: Series I comprised 15 Type A's (average age 49.3 ± 5.3(S.D.)) and 11 Type B's (50.9 ± 7.5 years); Series II comprised 19 Type A's (53.7 ± 7.5 years) and 10 Type B's (52.8 ± 8.9 years); Series III was constructed by selecting 13 hypertypical Type A's and 10 hypertypical Type B's from the two preceding series. Comparison between the Type A's and Type B's in two completely independent series (Series I and II) minimizes the possibility of statistical artifacts (see the Results section). Blood and urine samples were collected on an outpatient basis, as described below, and were frozen and sent to the Institute for Steroid Research (in New York) for analysis on a blind basis. Three of the Type A's and three of the Type B's also travelled to New York for 24-hour blood hormone studies on the Clinical Research Center at Montefiore Hospital. The New York investigators were blind as to the behavioral type of these subjects until after the steroid analyses had been completed.

Collection of blood and urine samples

Blood and urine were obtained from each subject over a period of three working days. 10ml of blood were taken at approximately 0900 and 1800 hours on the first two days (i.e. at the beginning and end of the normal working day) and at 0900 on the third day. The blood was allowed to clot and the serum was immediately removed by centrifugation and frozen until it was analyzed. Complete 24-hour urine collections were made during the three days, in 3 parts: from 0900 to 1800, from 1800 until bedtime and from bedtime until 0900. The samples were refrigerated without preservatives during the collection and were then frozen until they were analyzed. Completeness of urine collections was judged by the constancy of the creatinine excretion for the three 24-hour periods.

Analysis of urinary steroids

Aliquots from each subfraction of a 24-hour collections were combined to make a representative sample for that 24-hour collection. Each 24-hour sample was analyzed separately and the three results for each subject were then averaged. The three subfractions of the 24-hour collections were separately analyzed only for subjects in Series III (see below).

A small portion of each urine sample to be analyzed was directly treated with methylene chloride to extract free cortisol, which, after removal of the solvent, was measured by competitive protein-binding (11). Aliquots of urine were passed through an amberlite XAD column, which quantitatively removed the steroids (12). Elution of the column with methanol afforded complete recovery of the conjugated steroids. After evaporation of the methanol, they were dissolved in water and successively hydrolyzed by β-glucuronidase and mild acid treatment to cleave the glucuronides and sulfates respectively (13).

The steroid mixture from the extract of the hydrolyzed glucuronides was subjected to paper chromatography to separate the individual C-21 cortisol metabolites from the less polar steroids (14); the former were assayed by a quantitative blue-tetrazolium reaction. Urinary steroids obtained from the acid-hydrolyzed sulfates were further fractionated by the Girard procedure (13) to afford a ketonic fraction. The less polar glucuronide fraction was used for individual steroid analyses with no further purification.

Androgens were assayed by specific radioimmunoassay techniques. The androgens measured, in the glucuronide and sulfate fractions separately, were testosterone, dihydrotestosterone (DHT), 5α-androstan-3α-ol-17-one (androsterone), 5β-androstan-3α-ol-17-one (etiocholanolone) and 5-androsten-3β-ol-17-one (dehydroisoandrosterone). Testosterone and DHT were analyzed according to a modification of the method of Boyar et al (15), chromatographing the extract on a micro-column of celite to separate the two 17-OH androgens prior to binding with anti-testosterone antiserum. Another aliquot was passed through a small aluminum oxide column and the eluate was apportioned for binding with specific antisera against androsterone, etiocholanolone and dehydroisoandrosterone. In all radioimmunoassays, free steroid was separated from bound material by treatment with charcoal in buffer.

Analysis of the 0900-1800 sub-fraction of the 24-hour urine collections

We considered it possible that analysis of 0900-1800 urine collections might accentuate differences in steroid levels between Type A's and Type B's because these collections contain the products of the early-morning peak adrenocortical secretory activity and of the secretory activity during the working day, the period ordinarily associated with the greatest stress and tension. Therefore the 0900-1800 collections from the Series III subjects were separately analyzed by the same methods described above.

Analysis of plasma steroids

In the case of the outpatient studies, aliquots of the five serum samples were pooled for analysis, for two reasons: (a) the existence of episodic secretion of many hormones (16-19) results in rapid and profound fluctuations in their plasma levels: thus a pool of five widely-spaced samples over a 3-day period should yield more representative values than any single sample; (b) we considered it important to analyze all the samples from a given series in a single laboratory run, which would have been a physical impossibility if each individual plasma sample had had to be analyzed. Pilot studies with the individual plasma samples showed that none of the steroids except cortisol showed significant variation between samples and that the average of measurements in the five individual samples agreed closely with measurements in the pooled sample.

In the case of the 24-hour blood hormone studies, samples were drawn every 20 minutes around the clock, by means of an indwelling venous catheter; the technique has been described in detail elsewhere (16). Each of the 72 samples was analyzed individually for cortisol; 200 μg aliquots of each sample were pooled to make a 24-hour mean pool which was then analyzed for all the other steroids.

Cortisol was assayed by competitive protein-binding, using human transcortin as the ligand; free and bound steroid were separated with fluorisil (11). Testosterone and DHT were analyzed by radioimmunoassay (15), as described in the section on analysis of urinary steroids. Δ^4-Androstenedione was measured by radioimmunoassay, by the method of Baird et al (20). Radioimmunoassay techniques developed in this laboratory were employed for the measurement of DHA and DHA sulfate (19) and androsterone and androsterone sulfate (21). Briefly, these involved extraction of one milliliter of serum with benzene and chromatography of the extract on a small alumina column before binding with the appropriate antisera. For the sulfates, 25 μl of serum were solvolzyed with ethyl acetate-glacial acetic acid (22) prior to concentration and benzene extraction. Column chromatography was not necessary; portions of the same benzene extract were used for analysis of both androsterone and dehydroisoandrosterone since the antisera showed no cross-reactivity. Thyroxine and tri-iodothyronine were measured by radioimmunoassay, by methods developed in this laboratory (23).

Results

Plasma steroid concentrations (average of 5 samples over a 3-day period)

There was a consistent difference between Types A and B in both Series I and Series II with respect to dihydrotestosterone (Fig. 1). Combining both Series (Fig. 2), the geometric mean values (values were distributed log-normally) were 79 ng/dl for Type A and 93 ng/dl for Type B ($P < .05$). No other hormonal parameters differed in the two groups (Table I).

24-hour urinary steroid excretion

There was no difference in urinary steroid excretion (15 parameters) between Type A and Type B subjects that was consistent in both series (Table II). The excretion of dihydrotestosterone glucuronide was significantly higher in Type B subjects in Series I (73 vs 59 μg/day; $P < .05$), but there was no difference in Series II. It should be noted that if 20 parameters are measured in one series, there is a substantial possibility ($P = .05$) that one of them will show an apparent difference even though no real difference may be present. This type of artifact can be prevented by carrying out measurements in two independent series, as in this study; if this is done, the possibility that the same parameter will show an apparent difference in both series that is not real is very low ($P = .0025$).

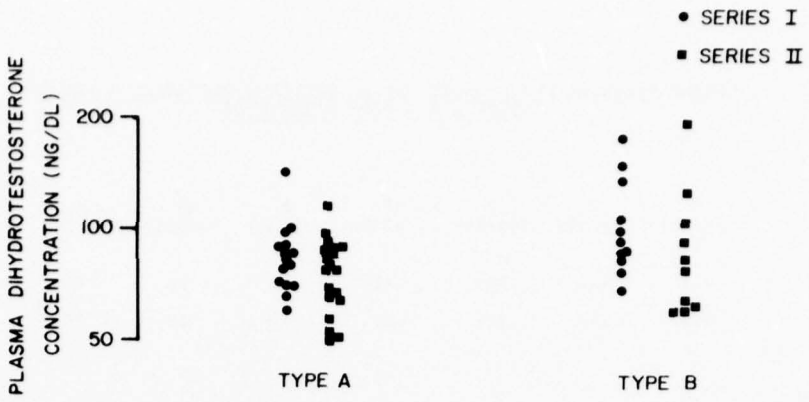

Figure 1 - Reproducibility of plasma dihydrotestosterone levels in two series of Type A and Type B subjects. There is excellent agreement between the two series in the range of values.

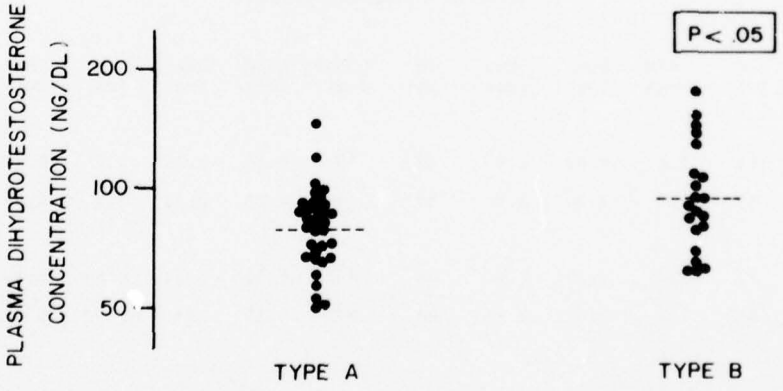

Figure 2 - Plasma dihydrotestosterone levels in Type A and Type B subjects. The values shown represent Series I and Series II combined.

Table I

PLASMA STEROIDS WHICH SHOWED NO SIGNIFICANT DIFFERENCES BETWEEN TYPE A AND TYPE B SUBJECTS

SUBJECTS	F (µg/dl)	T (ng/dl)	D (ng/dl)	DS (µg/dl)	A (ng/dl)	AS (µg/dl)	Δ (ng/dl)	T_3 (ng/dl)	T_4 (µg/dl)
Series I									
Type A	9.3	527	386	141	77	86	61	133	6.2
Type B	9.2	654	423	137	82	68	59	134	6.4
Series II									
Type A	10.6	537	288	150	65	49	61	-	-
Type B	9.7	549	293	139	62	64	59	-	-

F = Cortisol; T = Testosterone; D = Dehydroisoandrosterone; DS = Dehydroisoandrosterone sulfate; A = Androsterone; AS = Androsterone Sulfate; Δ = Δ^4-Androstenedione; T_3 = Tri-iodothyronine; T_4 = Thyroxine

Table II

24-HOUR URINARY STEROID EXCRETION IN TYPE A AND TYPE B SUBJECTS

SUBJECTS	F (µg)	THF (mg)	ATHF (mg)	THE (mg)	TG (µg)	DHTG* (µg)	DHAG (mg)	DHAS (mg)	AG (mg)	AS (mg)	EG (mg)	ES (mg)
Series I												
Type A	68	2.4	0.90	2.9	52	59	0.13	0.34	1.7	0.51	2.5	0.34
Type B	65	2.1	1.0	2.9	57	73	0.08	0.29	2.2	0.38	2.7	0.25
Series II												
Type A	82	1.9	0.57	2.6	46	44	0.11	0.24	0.84	0.40	2.2	0.24
Type B	81	1.8	0.44	2.2	48	42	0.17	**	0.93	0.43	2.7	0.35

F = Cortisol; THF - Tetrahydrocortisol; ATHF = Allotetrahydrocortisol; THE = Tetrahydrocortisone; TG = Testosterone glucuronide; DHTG = Dihydrotestosterone Glucuronide; DHAG = Dehydroisoandrosterone glucuronide; DHAS = Dihydroisoandrosterone sulfate; AG = Androsterone glucuronide; AS = Androsterone sulfate; EG = Etiocholanolone glucuronide; ES = Etiocholanolone sulfate;

* Significant difference between Type A and B in Series I ($P < .05$) but not in Series II

** Heterogeneous population: two subjects showed values 10 and 50 times the normal mean value; this is believed to be a genetic variant unrelated to the Type A - Type B dichotomy.

0900-1800 urinary steroid excretion

The subjects in Series III showed a significant difference in the 0900-1800 excretion of testosterone glucuronide: the geometric mean value was 24 µg for Type A's and 15 µg for Type B's ($P < .05$)(Figure 3). A nearly identical difference was found between the mean of the 0900-1800 excretion values for the 15 Type A and 11 Type B subjects of Series I (23 and 14 µg respectively), but the individual samples were not analyzed so that a statistical evaluation of the significance of that difference is not possible.

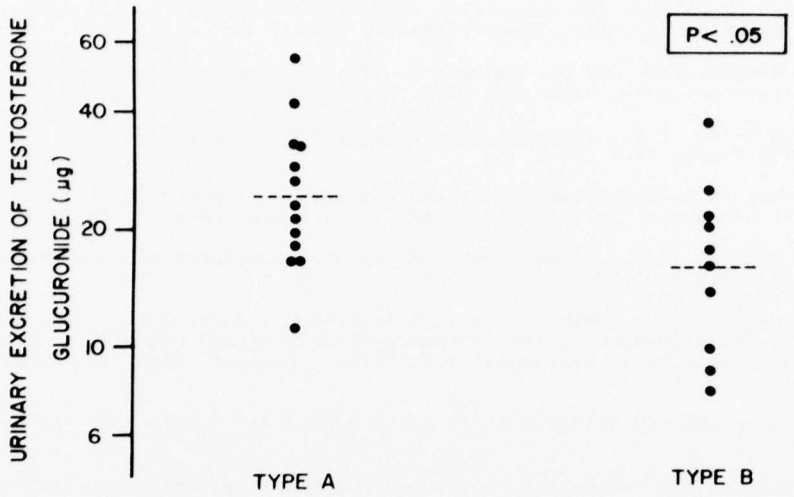

Figure 3 - Daytime (0900-1800) urinary excretion of testosterone glucuronide in Type A and Type B subjects. The values shown represent Series III.

24-hour mean plasma steroid concentration (Table III)

There were no significant differences between Type A and Type B subjects with respect to any of the nine steroids measured, not surprising in view of the small number of subjects studied. Despite this, it is noteworthy that all six of the androgens (testosterone, dihydrotestosterone, dehydroisoandrosterone, dehydroisoandrosterone sulfate, androsterone and androsterone sulfate) showed higher levels (by 10-64%) in Type B's than in Type A's. The probability that this would occur by chance is quite low ($P = .0156$ by Fisher's exact test). It is of interest that this small series of 24-hour studies also confirmed a difference with respect to plasma dihydrotestosterone concentration: 39% higher in Type B's in this series compared with 18% higher in Type B's in the combined Series I and Series II.

Discussion

The studies we are reporting showed two steroidal differences in the area of androgens, between men with the Type A behavior pattern and those with the Type B pattern: Type A men had lower average plasma concentrations of dihydrotestosterone and higher daytime urinary excretion of testosterone glucuronide than Type B men. The fact that these differences involve sex hormones is not without possible significance: men have a much higher incidence of CHD than women, and it has been suggested that hormonal differences between the sexes may be related to this clinical difference. Higher urinary excretion of testosterone glucuronide in Type A men may indicate greater testosterone production and/or higher plasma levels of non-protein-bound testosterone in these men. The physiological significance of higher plasma dihydrotestosterone levels in Type B men is not obvious, but it is of possible pertinence that the dihydrotestosterone/testosterone ratio is many times greater in women than in men. Supporting the possible significance of the sex hormone levels for CHD are animal studies which have shown that testosterone increases and estradiol decreases arterial wall hypertrophy in response to experimental hypertension (24,25) and that testosterone increases and estradiol decreases arterial thrombosis after intimal injury (26).

Whatever the detailed mechanisms by which the sex hormones may be involved in the genesis of or protection against CHD, one clear-cut fact emerges from the present study: two groups of men selected purely because of clinically determined differences in their behavior patterns also differed with respect to certain plasma and urinary parameters of androgenic steroid hormones. If these steroidal differences are at all related to the differing risks for CHD of these two groups of men, the present findings point towards a way of intervening to decrease the higher risk of Type A men, by changing the levels or antagonizing the effects of certain steroid hormones.

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Table III

24-HOUR MEAN PLASMA STEROID CONCENTRATIONS IN TYPE A AND TYPE B SUBJECTS

SUBJECTS	F (ug/dl)	T (ng/dl)	DHT (ng/dl)	D (ng/dl)	DS (µg/dl)	A (ng/dl)	AS (µg/dl)
Type A	9.1	325	81	249	57	52	27
	7.3	452	127	262	55	55	18
	8.3	514	96	395	143	74	55
Mean	8.2	430	101	302	85	60	33
Type B	7.6	501	152	539	128	90	95
	7.9	576	139	541	150	82	31
	7.5	337	130	282	62	89	37
Mean	7.7	471	140	454	113	87	54

Abbreviations as in Table I

DISCUSSION

Troxler: Dr. Zumoff, did you consider Dr. Friedman's observations where he found a difference in the ACTH secretion between type A and type B individuals?

Zumoff: I am familiar with Dr. Friedman's original paper. Dr. Friedman was interested in the possibility that cortisol changes mediated these differences. His approach was to measure cortisol metabolites in the urine comparing type B and type A individuals. He found no differences, as we have not. I dare say without having discussed it with him that he was disappointed at that time and said, "No it can't be, there has got to be some kind of a difference". He then did ACTH loading in these individuals and observed that type A individuals showed a somewhat smaller response to ACTH than did type B. This is a little backwards from what we were hoping would be the case from recent observations. I must tell you I am not impressed that it was a definitive study. I think that kind of thing has to be done again. Perhaps that work has been made obsolescent by what I think are more germane studies, such as those you have already done.

ROUND TABLE DISCUSSION

Triebwasser: From our discussions, it is obvious that we all share the same problems and agree on some major issues. I think we are all in agreement that it is important to identify a population at risk for sudden incapacitation. Coronary artery disease is the major problem confronting our aircrews. Our aircrew members are older now than they were 15 or 20 years ago. We all agree that our methods for identifying fliers at risk are poor and therefore we need more definitive noninvasive methods for identifying those at risk and began an active intervention program which hopefully will prevent disease progression, to a point, when it becomes clinically manifest as a coronary event. Unfortunately at this point in time, we don't have any clear cut evidence that alteration s of risk factors will alter the progression of the disease. However, more and more evidence is accumulating which suggests a greater role for preventative medicine within the immediate future. We all agree that we are having much difficulty defining what is normal. When does a 4th heart sound signal underlying heart disease and when is it a normal finding? What is the significance of a ventricular premature beat? What is the meaning of abnormal response to a given stress test? Finally, we also agree that we have difficulty defining when we should treat a given condition such as hypertension.

We have some disagreements. For example, we can not define acceptable screening procedures for use in our aircrew population. These disagreements really are related to the types of population we serve, which range from civil air transport pilots to the military high performance jet fighter pilots. Cost versus yield of these various tests must also be considered. Most of us agree that the resting electrocardiogram and the history and physical examination, can miss significant disease. Many of us would like to employ a stress test that would identify an individual at risk. But we disagree in terms of how we should interpret the results. For example, should an abnormal stress electrocardiogram result in our submitting that given aircrew member to coronary arteriography?

There are four major topics that I wish we had time to spend another day or two discussing. These include: 1) The problems of coronary disease detection. What routine screening tools should one use to detect the disease and when should we employ coronary arteriography? 2) Cardiac arrhythmias are another important area for discussion. What rhythm disturbances are benign versus what are malignant? How should we evaluate an individual who presents with ventricular premature beats as a new finding? We need more discussion in terms of when we should treat arrhythmias and more definitive guideline for aeromedical decisions. 3) Hypertension is another major area for discussion. We cannot define what is a normal blood pressure. As a result we have difficulty defining when and how we should treat a flier who has high blood pressure. 4) Finally we need to clarify a cost effective approach to risk identification. Such a program should be implemented, and how the results should influence aircrew selection and retention criteria. These are major areas all of us face. Unfortunately, we do not have a crystal ball available to answer the questions generated by these problems.

Now to begin our discussion, I would like us to consider the role of exercise electrocardiography. We have heard several opinions that some would argue represent extreme viewpoints. These are really not extreme viewpoints because they are well founded and represent our individual problems related to the unique population we serve. Some of us feel that we should not do exercise stress testing as a routine tool because we have the problem of false positive tests. Others of us on the other end of the scale suggest we should use this test routinely and anyone who has an abnormal response, should undergo coronary arteriography. Are there any other things we can do to help us interpret the exercise stress test? Should we use the presence or absence of other risk factors in making this determination?

Kelly: Regarding the use of exercise electrocardiography as a routine procedure, I think one has to bear in mind a paper published about three or four years ago in the Aerospecial Medical Journal in which it was postulated (I can't actually remember the exact figures), that if this were done in everybody there would still be a greater absolute number of coronary incidents occurring in those people with negative tests than in those with positive tests, purely because they are much the greater population. I think it was something like ten times the number.

Lancaster: I think we have a perplexing problem. On the one hand we are all concerned about coronary disease detection and I think all of us would be at the extreme of not being content to ignore this problem completely, or to rely on a standard history and physical examination and a resting electrocardiogram. But, at the other extreme, we can't cope with the entire problem that is produced by doing every thing possible. We don't have the manpower or other resources to do all of the techniques, even those that have been presented here at this meeting. Additionally, if we do attack the problem in terms of making diagnoses by using a battery of tests, we will turn up false positive tests with which we must cope. That creates a major problem. I think we should approach the problem today with sort of an idealistic philosophy. I personally think that the way to deal with this problem is with prevention and I doubt that I would get much argument there. The argument would come in whether we can actually do anything to prevent the disease. I personally think we can and should. Furthermore, I think that to start a coronary disease prevention program after people have developed symptoms is way too late. It is clearly too late for a third of the people in the United States because all they need is a funeral. It is perhaps too late in 65% of the people of the United States because they would have had a myocardial infarction. I have serious reservations as to how much we can accomplish in people who have well established disease with respect to insuring their longevity or improving their basic disease process. So, in a sense I am willing to ignore people in my age group and older and say it is just about too late for us, and emphasize working with younger individuals. Now that presents another problem, we

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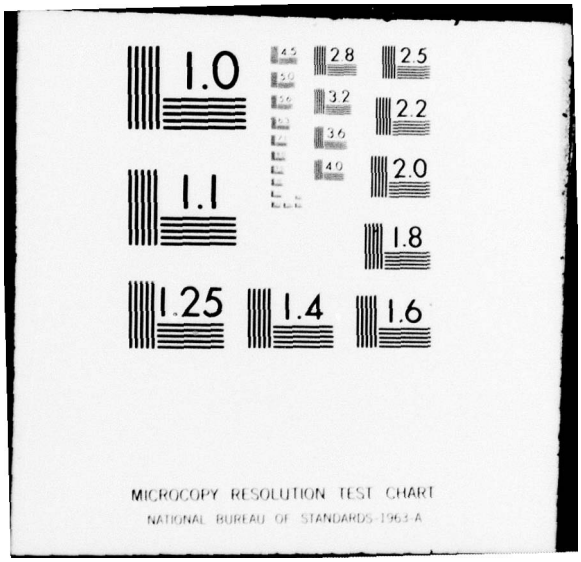
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won't know whether we have done very much good for 20 years or so. That's a long time and makes a prevention program difficult to sell and get the necessary resources. We have, I think, successfully done that in the United States Air Force; at least we have been able to sell the current Air Staff on the idea to attack the younger individual. At the moment I would approach the aircrew with a battery of known and well established tests for risk factors, and screen those individuals who are at some increased risk level with more elaborate tests, such as exercise stress testing, and if positive, I would do coronary angiography. I'll add a further note, perhaps to generate some discussion, and that is, I believe those individuals who have significant coronary disease deserve consideration for surgery, even though they are asymptomatic. If we wait until people develop symptoms many will have lost considerable myocardium and/or their lives. So, the idea of waiting till you get symptoms before considering surgery is to me flaunting in the face of logic.

Triebwasser: I would like to summarize what you just said. You said you would employ exercise electrocardiography. If the tests were positive you would perform coronary arteriography, and if the individual were found to have high grade disease, you would recommend that individual be referred for bypass surgery. Those statements should generate further discussion.

Fitzgibbon: Well for me Dr. Triebwasser, it wouldn't generate any argument at all. I agree completely with Col Lancaster. Having had some primacy in the world of my own hospital in referring patients who are asymptomatic for myocardial vascularization surgery, I don't think it makes any difference at all whether you have symptoms in determining whether or not you are a candidate for bypassing a stenosis in a coronary artery. I think we have some very strange ideas about bypassing coronary arteries. We found it perfectly acceptable to bypass other vessels without any question. What I'm trying to get at is that I think that the cause of understanding and properly dealing with coronary artery disease would be best served if we stopped calling it coronary artery disease, because this makes it a kind of mysterious sacred disease, one in which we know nothing and do very little. I think it would be much better if we talked about coronary stenosis in the same way that we came about to talk about mitral stenosis rather than mitral valve disease. That is really the water shed between doing something and not doing something. I think we remember from our teaching days, when it was considered socially unacceptable to even consider the possibility of doing a mitral commissurotomy because everybody knew that patients with mitral stenosis died from rheumatic disease of the myocardium, certainly not because they had mitral stenosis. The same is true with coronary stenosis. Bypass surgery should be done to deal with a lesion, not to deal with a symptom. Now, I have some experience in following up patients on a regular basis who have had bypass surgery and doing angiography. I do assure you that it is very important in these people to control the so-called risk factors. If you do succeed in controlling these you do see a halting of the progession of the coronary plaques. In patients who do not follow the rules, in patients whose hypertension is not controlled, in patients who do not stick to their diets qualitatively or quantatively, in patients who go back to smoking, we see progression of disease including new disease and worsening of previous disease. This is in patients who have already been operated on. So, we are dealing with a chronic disease in which surgery is merely an acute intervention to deal with one complication, a very important one, that of coronary stenosis. Now as to the question of the exercise stress test, I'm not really personally concerned very much about the false positive tests, because I do have somewhere to go from there. I can take the patient to the cardiac catheterization laboratory and do a coronary angiogram. It is really the coronary arteries that we are interested in, not the squiggle on a piece of electrocardiographic paper. My concern is very, very much with the false negative tests. My concern is with the patient who comes to us with some other kind of flag. He has had a bout of curious chest pain a few months ago, and none since. He had a small myocardial infarct three months ago but he is totally asymptomatic now and has a negative treadmill test. The question then is whether or not to do coronary angiography in these people with negative treadmill tests. We do coronary angiography and very frequently we find very severe disease in the complete absence of an abnormal progressive exercise test of the types mentioned earlier in this conference, in an important proportion of subjects. So, there is no question in my mind that we should proceed the whole way to investigate these people. There are other sorts of things that help you make a decision; for example the time honored lipid studies bearing in mind what has already been discussed about the blood cholesterol earlier today. I would like to draw your attention to two factors that have not been mentioned at any time during these meetings and they are really quite important. Some predictive formulae take into account the vital capacity and note that the higher the vital capacity the less likelihood there is for the presence of coronary disease. And lastly, I would like to tell you that if I had at my disposal a laboratory that could supply me with only one biochemical measurement, the one that I would use would be the blood sugar two hours after 100 gms or 1.0 gm/kg of glucose. There is a tendency to correlate coronary artery disease incorrectly with diabetes. I think the proper correlation is not with diabetes as defined by the American Diabetic Association, but with glucose intolerance. A reference ready guide is a true blood sugar of 120 mg% or more, two hours after a loading dose of sugar. This correlates much greater with the presence of angiographically demonstrated coronary artery disease than does the blood cholesterol or the serum triglyceride in the population in which I study, having a mean age of about 34.

Triebwasser: In our experience the reproducibility of blood glucose measurements is no better, perhaps worse than that for cholesterol and triglycerides.

Zumoff: I would like to make another comment. A number of people have mentioned that they are a little bit pessimistic about the dent exercise stress tests make in picking out the patients with coronary disease. I think it is not quite as pessimistic as has been suggested. For example, if 5.0% of the population you study has a positive exercise test and their increased

risk, let's say for the sake of argument, is 20%, that means that 50% of the anticipated events will occur in the particular group having a positive stress test. Therefore if you could remove all those individuals that would make an enormous dent especially when one considers the fact that those statistics refer to a single study. What if you did it every year and you picked up the incremental people who don't have a positive stress test this year but will have one next year or the year after that? I would suggest that given these known statistics and as a result you were to ground everybody who had a positive exercise stress test, you could conceivably eliminate upwards of 50% of those who are going to have coronary events.

Triebwasser: To change topics, I would like to ask what beta-blocker should one use for treating hypertension in the aircrewmember? This discussion this morning really disturbed me in terms of the beta-blockers' effect on the central nervous system. It was suggested that an individual's appreciation for impending stress is somewhat blunted while on these medications. Is he therefore at increased risk in terms of flying safety? I would like to ask Dr. Cooke if he feels that we can use beta-blockers in the treatment of hypertension, especially in the case of the high performance fighter aircraft pilot?

Cooke: The choice of a beta-blocker is extremely difficult at this moment. The experience that we have in the UK, over 10 years, has been primarily with propranolol and to a great extent with oxprenolol in the last six or seven years. I would remind you gentlemen that originally these drugs were not introduced for the treatment of hypertension. They were used mainly to reduce the oxygen requirement of the heart in ischemic heart disease and angina, and really their use in hypertension came along secondarily. So we haven't got anything like the same experience in hypertension that we have in the smaller doses that were used for angina. The drug that we know most about from the side effect standpoint is propranolol, that is the mixture of dextro and levopropranolol. We do know that propranolol has dose related central nervous system effects on behavior, on accuracy, on powers of concentration, and on a number of other factors. We also have the problem, and it must be familiar to all of you working with hypertension, that a hypertensive is a fit man until you treat him. In fact, I often wonder whether hypertensives are not more than fit; they are almost in overdrive. At the moment you give them any kind of drug which reduces their blood pressure, you reduce their feeling of overdrive and of well-being. From that time onwards, you have a problem in assessing what are the specific effects of the drug and what may be the specific effects of altering the man's hypertension. If I am pressed in a corner, I would say that at the moment I believe that if one is going to treat members of aircrew with a beta-blocker, one should use the drugs which have been shown not to have serious long-term side effects. Those two drugs, despite their disadvantages on central nervous action, would be propranolol and oxprenolol. Many of their side effects are dose-related. Therefore, only those members of aircrew who need small doses of these drugs should be allowed to fly and only after a good and satisfactory prolonged study on the ground. That would be my present position. Studies with propranolol and oxprenolol have been conducted and it appears as though the small clinical doses of up to 80-120 mg, are not really associated with a high incidence of side effects. I don't think I have to tell such an experienced audience that people will get side effects with much smaller doses than that, idiosyncratically. One thing is for sure, no hypertensive should be asked to fly taking a drug which he, the subject, believes is doing him harm. If he believes that, whether it would be on a good sound basis or not, he should not fly taking it.

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14. Abstract

Prospective medicine seeks to identify the propensity for disease development at a stage long before clinical pathology can be detected and thus enables the delivery of medical care well beyond the current concepts of preventive medicine.

Specific identification of risk factors stimulates the modification of risk through specific education and clinical efforts.

The prospective medicine approach could form the basis for significant revision of selection and retention criteria for the military aircrew.

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