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THE ROLE OF THE CLINICAL LABORATORY IN AEROSPACE MEDICINE

Edited by

Lt Colonel Raymond G.Troxler, USAF, MC
Chief, Clinical Pathology Branch
Clinical Sciences Division
USAF School of Aerospace Medicine (AFSC)
Brooks Air Force Base, Texas 78235, US

Papers presented at the Aerospace Medical Panel Specialists Meeting
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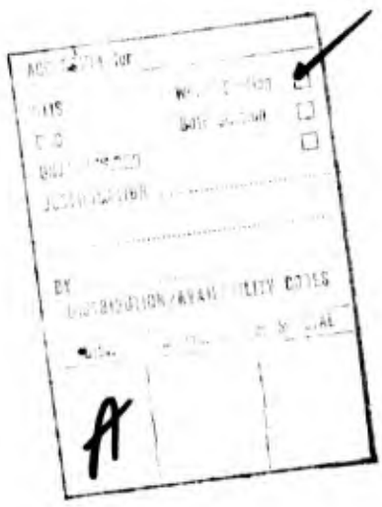

SUMMARY

This Conference has pointed out the need to understand the limitations of our clinical laboratory tests both old and new. We must pay particular attention to the sources of variation of these tests. The expected incidence in our flying population of positive tests such as the standard glucose tolerance test, EEGs, and tests of hemostasis has been reported. The laboratory assessment of stress in air traffic controllers, army artillery men, and aircrewmen has been documented and should be extended.

This Symposium has emphasized the need for physicians in the practice of Aerospace Medicine to learn to detect early disease in order to assure better selection of aircrews, as well as the need for early medical intervention to maintain aircrew effectiveness in a highly stressful environment. It has shown that to be cost effective laboratory screening must be done for those diseases most likely to affect flight operations. We therefore are encouraged to test aircrews for common diseases such as coronary atherosclerosis. Although detection of subclinical disease is a difficult task, we must not shrink from our responsibility as aeromedical specialists to our aircrews and to humanity.

PREFACE

The clinical laboratory is indispensable in the practice of aerospace medicine. The optimal tests, techniques and procedures, along with their clinical correlations for judicious application are matters of continuing research and development. Application of the results of this meeting should improve diagnostic accuracy, enhance utilization of diagnostic resources, and provide increased impetus toward standardization of clinical laboratory methods in aerospace medicine in the international community.

Papers were invited on the following topics:

(1) Investigations on chemical, physical, physiological, radiographic and electrical test techniques, methodologies and applications in aerospace medicine.

(2) Research, development and evaluation of pertinent tests, techniques and procedures in aerospace medicine.

(3) Results of clinical and epidemiological application of these tests, techniques and procedures.

(4) Limitations of the tests, techniques and procedures due to variability, interference, inadequacies, etc.

CONTENTS

* Paper not presented.

TECHNICAL EVALUATION REPORT

The AGARD-NATO Aerospace Medical Panel Specialist Meeting on "The Role of the Clinical Laboratory in Aerospace Medicine" was held in Ankara, Turkey, 20 to 24 October 1975.

Sixteen papers were presented. The authors discussed biochemical, physiological, psychological, and radiological measurements which aid the aeromedical specialist in the early detection of disease. A summary of the discussion and the participants in the discussion can be found at the end of each paper.

The presentations were in three main categories:

1. The role of the clinical laboratory in measuring the stresses of the operational environment on the personnel involved in flight operations: A7, A8, A9, and A10.

2. A reassessment of existing laboratory tests which will make them more effective in documenting the early changes of disease in flying personnel: A1, A2, A3, A4, A11, A12, A13, A14, A16 and A17.

3. An evaluation of the capabilities and limitations of recently developed clinical laboratory measurements which can aid the aeromedical specialist in his studies on the hormonal changes in disease and the effect of aging in the flyer: A6 and A15. Paper A5 was not presented.

CONCLUSIONS AND RECOMMENDATIONS:

These presentations reaffirm the vital role of the clinical laboratory in measuring the stresses of the flight environment and in simulated flight environments. Several new clinical measurements such as a radioimmunoassay (RIA) were discussed. The ability of the aeromedical specialist to measure hormonal changes in diseases is now unending with the advent of RIA. Its limitations must be carefully studied to derive valid data.

It was documented that psychological stress can alter hormone levels in aircrew members. A mathematical index of stress can be derived from measuring "stress hormones". This model is apparently correlated with the level of difficulty of performance of duty in air traffic controllers in the United States.

In the discussion of these papers on stress the conferees stated that previous studies have shown that levels of stress hormones are much higher in student pilots than in experienced pilots (even experienced pilots in combat). The question was raised can increased levels of stress hormones be correlated with lack of flying proficiency. This is an interesting point which should be explored in greater depth. H. B. Hale and coworkers at the USAF School of Aerospace Medicine reported an inverse relationship between stress hormone levels and flying proficiency in 1965. Follow-up studies on combat pilots had conflicting results. A well defined study of stress hormone levels in student pilots before and after flying training correlated with their flying proficiency seems in order.

As the technology of aviation advances, man is called upon to extend himself to the limit of his ability to perform. Subclinical diseases which would not affect an individual's average performance may well affect this individual when stressed to the limits of his capabilities. The aeromedical specialist should now accept the challenge of attempting to detect subclinical diseases. An invaluable tool at his disposal is the clinical laboratory. Measurements designed to detect subclinical disease must necessarily be very sensitive. As sensitivity increases, often the number of false positive laboratory tests increase. This effect is multiplied by the number of sensitive tests the aeromedical specialist performs. For this reason routine laboratory screening of asymptomatic individuals for all diseases is not cost effective. Rather the aeromedical specialist must choose those diseases which are most likely to impair flight operations and screen for them. For example, coronary atherosclerosis is one such disease. Its prevalence by autopsy studies increases from 30% to 90% during the average flyer's twenty year tour of duty.

Once the disease to be detected is identified we must then identify and minimize the sources of variation in the laboratory tests selected to detect the disease. The sources of variation due to the laboratory alone such as specimen collection, specimen handling, and the imprecision of the test must be held to a minimum. Sources of biological variation such as age, sex, date, time of day, etc. should be held constant if possible. Only when all sources of variation are minimized or held constant and the main source of variation is due to disease can we adequately define the normal range of a laboratory test.

The problem of defining normal patients when studying coronary artery disease is especially difficult because the disease usually causes symptoms only when very severe. Abnormals are often placed in a "normal" category. Coronary angiography to date is the best available tool for defining patients with and without coronary artery disease. Defining the true disease state in terms of subclinical diabetes mellitus and EEG abnormalities are more difficult. The only possible

solution appears to be carefully controlled long term follow-up studies. In the future proper control of laboratory and biological variation coupled with well defined disease end points should allow the prediction of disease from physiological and biochemical measurements in the laboratory of the aeromedical specialist.

The Laboratory Role in Early Detection of Disease

John Bernard Henry, M.D.
Professor of Pathology
Director of Clinical Pathology
State University of New York
Upstate Medical Center
750 East Adams Street
Syracuse, New York 13210

The laboratory has a unique role as well as virtually unlimited opportunities to participate in the early detection of disease. Indeed, this role is clearly identified among the five objectives of laboratory medicine as follows:

1. Diagnosis
2. Rule out or exclusion of a disease
3. Prognosis
4. Therapeutic guidelines
5. Screening

In regard to screening, two important aims are incorporated. First, the individual's normal values may be defined and indeed delineated by periodic clinical pathologic measurements and examinations. From such individual normal values, narrower limits approximating one-third of the population-defined normal ranges for a particular measurement may be observed for multiple determinations. With such narrower individual normal ranges, it is possible to identify a disease, i.e., deviation from normal much earlier or in a more sensitive manner than when accomplished through the application of population normal values.

The second aim of screening is detection or identification of disease prior to the onset of symptoms or signs. As mentioned previously, however, when population normal values are applied for identification of disease, sensitivity is reduced considerably in contrast to the utilization of the individual's normal values. Obviously, the early detection of disease depends upon prevalence of disease in a defined population. In other words, the maximum utilization of the laboratory in early detection of disease should reflect those diseases which are more frequent in a population by virtue of age, sex and other criteria.

Utilization of laboratory measurements and examinations in detection of disease requires a keen appreciation of the usefulness of a positive determination which will vary with the sensitivity and the specificity of the particular determination as well as with the incidence of the disease in the population tested[1]. By sensitivity I mean the percent of positive results in patients with disease. For example, the screening test for phenylketonuria is highly sensitive and all patients with the disease will reveal a positive result, i.e., 100 percent sensitivity. Other measurements have lesser or varying sensitivity; for example, the serum thyroxine may be extremely sensitive, i.e., detect 100 percent of patients who are hypothyroid with low T_4 values. However, patients who are borderline hypothyroid, i.e., nonspecific symptoms plus an elevated level of thyroid stimulating hormone (TSH) will show a depressed level of serum T_4 in less than 80 percent. We should also recognize that specific tests which are highly sensitive, i.e., 100 percent, at one stage of a disease will be less sensitive in early disease, e.g., serum creatinine and renal disease. Thus, a negative measurement or examination on a laboratory screening test may provide a false sense of security or even lead to neglect of a finding on history and/or physical examination for a determination that is 100 percent positive in advanced disease but only 20 percent positive in the early stages of the same disease. It appears then that sensitivity in early disease seldom equals that reported in studies based on proven cases[1].

A laboratory measurement's specificity refers to the percent of negative results among individuals who do not have the disease for which a screening measurement is performed. For example, the test for phenylketonuria is highly specific, i.e., 99.9 percent of normal individuals have a negative result (99.9 percent specificity). The serum thyroxine measurement is highly specific in distinguishing normals from hyperthyroid individuals, but there is considerable overlap between normal pregnancy and women on oral contraceptive agents and hyperthyroid states because of variations in levels of thyroxine binding globulins. Thus, specificity will vary with the control group used. In other words, specificity may be less than scientific reports depict when these are based on "normal control groups".

A third term emphasized by Krieg and colleagues recently is the predictive value of a positive measurement or examination. A predictive value of a positive measurement defines a percentage of positive results that are true positives. Hence, the predictive value will vary with sensitivity, specificity and incidence. Indeed, incidence plays a most important role in understanding how sensitivity and specificity affect the predictive value. This may be illustrated by considering a measurement with 95 percent sensitivity and 95 percent specificity in two different populations, one with a disease incidence of 10 percent and the other with a disease incidence of only one percent. With a measurement displaying 95 percent sensitivity and specifi-

city, the population in which the incidence of disease is 10 percent from data collected on 10,000 subjects, one can note that of the 1,400 positive results, 450 are false positives[1]. Thus, the predictive value of a positive result is only 68 percent because 950 of the 1,400 positive results were true positives as follows:

Subjects	No. With Positive Test	No. With Negative Test
1,000 Diseased	950	50*
9,000 Non-diseased	450	8,550**
TOTAL	1,400	8,600

*Sensitivity, 95%.
**Specificity, 95%.

In contrast, if the incidence of the disease is one percent, the predictive value is considerably less as shown by identification of 590 positive results with only 95 true positives:

Subjects	No. With Positive Test	No. With Negative Test
100 Diseased	95	5*
9,900 Non-diseased	495	9,405**
TOTAL	590	9,410

*Sensitivity, 95%.
**Specificity, 95%.

In this example, the predictive value of a positive result is only 16 percent[1]. In other words, specimens yielding a positive result have only one chance in six of reflecting the disease. What about the effect of incidence on the predictive value of a positive result? Measurements with a high degree of sensitivity and specificity when applied to a population with a higher incidence of disease, for example, serum creatinine on the urology service would have a higher predictive value. A two-hour postprandial glucose determination will have a higher predictive value in subjects with a family history of diabetes than in those without such a family history. Furthermore, a serum T_4 value will have a higher predictive value in women with classical symptoms of hypothyroidism, i.e., dry skin, lethargy, slow speech and cold intolerance than in the general or well population. Therefore, the problem of screening requires a clearcut appreciation of the complex interrelations of sensitivity, specificity and incidence.

An approach to the laboratory role in early detection of disease that I will pursue is age span and most prevalent diseases that are most likely to be detected by specific measurements and examinations of blood and other body fluids[2]. However, caution must be expressed regarding the implications of genetic screening in terms of the nature and consequences of a particular program, cost effectiveness, scientific accuracy, and available or effective treatment for persons having "screened for conditions"[3].

Type II hyperlipoproteinemia has been delineated in cord blood of newborns with triglyceride measurements and subsequent lipoprotein electrophoresis. From primate studies, it appears that atherosclerosis associated with type II hyperlipoproteinemia may be preventable and indeed even reversible with appropriate management. Galactosemia associated with a deficiency of galactose-1-phosphate uridyltransferase may be identified in newborns also with appropriate red cell hemolysate measurements. The consequences of this disease in terms of cataracts and hepatic degeneration can be avoided by early detection and avoidance of galactose in the diet.

Hemoglobinopathies represent a variety of illnesses in terms of inborn errors of metabolism and genetic implications for which early laboratory diagnosis has proven techniques available. Screening for sickle cell disease and subsequent hemoglobin electrophoresis clearly delineates both the carrier as well as the homozygous (SS) state. Other hemoglobinopathies generally initiated subsequent to identification of anemia likewise can be identified through comparable studies of hemoglobin electrophoresis and alkali resistant hemoglobin. An excess of hemoglobin or hematocrit may be associated with either primary or secondary polycythemia.

Serum protein electrophoresis may be invaluable, particularly when it is coupled with immunoelectrophoresis in the delineation of immunoglobulin deficiencies most frequently associated with hypogammaglobulinemia, but also with IgA and others. Likewise, hyperproteinemia, particularly in multiple myeloma and macroglobulinemia, may also be displayed by laboratory total protein measurements and protein electrophoresis with the particular protein delineated by immunodiffusion in terms of the gammopathy subsequent to electrophoresis. In allergic states, the IgE measurement may be useful. Cirrhosis of the liver is often associated with a diffuse hyperglobulinemia and depressed albumin.

The prediction of hemolytic disease of a newborn on the basis of the ABO or Rh incompatibility can be ascertained through appropriate prenatal and neonatal immunohematologic studies.

Connective tissue diseases, particularly lupus erythematosus as well as rheumatoid arthritis, lend themselves to specific measurements such as antinuclear antibodies (ANA) and the LE preparation while the tests for rheumatoid factor have a high degree of sensitivity in rheumatoid arthritis afflicted patients.

In terms of gout and hyperuricemia, measurements of serum uric acid would be most sensitive in terms of early detection in males as well as post-menopausal females. Wilson's disease may be detected in individuals by ceruloplasmin measurements but obviously would be more sensitive in individuals who have evidence of hepatic disease and/or Kayser-Fleischer rings. A host of lipid and metabolic disorders including hyperlipoproteinemia types I - V may be delineated through appropriate measurements of serum cholesterol and triglycerides with subsequent lipoprotein electrophoresis for delineation. Delta amino-levulinic acid is an optimal screening test for acute intermittent porphyria as well as an elevation of coproporphyrin in lead poisoning. However, in lead poisoning we now recommend measurements of blood lead for screening susceptible populations.

We have already alluded to delineation of hyper- and hypothyroidism with serum TSH for the latter and serum thyroxine or free thyroxine for the former. In hyperparathyroidism, the serum calcium is the most sensitive single determination; this has been well documented in screening hospital population groups where an elevated calcium is most often associated with a low serum phosphorus although hypophosphatemia is not invariable. Even though the most common cause of hypercalcemia is a non-parathyroid neoplasm, Boonstra and Jackson[4] in 1971 reported a ratio of one case of hyperparathyroidism per 1,000 individuals surveyed, i.e., about 50 cases in 50,000 clinic patients over a 10-year period. When these workers performed serum calcium measurements for the relatives of all patients with hyperparathyroidism found in their survey, an additional 24 patients in seven families with hyperparathyroidism were identified. Hypocalcemia may be associated not only with hypoparathyroidism, but with a depression of serum protein concentration. Neonatal hypocalcemia appears to be associated with diabetes, prematurity and other complications of pregnancy that are often ascribed to inadequate development of the parathyroid gland. Medullary carcinoma of the thyroid patients may have high serum calcium levels usually without any abnormality of calcium metabolism but thyrocalcitonin elevations. In the early detection of disease, the loss of diurnal variation of plasma cortisol levels may be one of the incipient manifestations that subsequently evolves to sustained elevated plasma cortisol and lack of suppression. Likewise, in Addison's disease there is a depression of plasma cortisol and urinary free cortisol. For hypertensive patients, laboratory evaluation often involves not only VMA (Vanillylmandelic Acid), but also catecholamines and serum electrolytes to delineate the particular abnormality.

In diabetes mellitus where the fasting blood glucose is the least sensitive measurement in early disease, the one-hour postprandial glucose has the highest sensitivity but with lesser specificity in contrast to the two-hour postprandial glucose which has greater specificity but slightly less sensitivity.

At the State University of New York, Upstate Medical Center we have assembled medical problem oriented panels of measurements and examinations that enhance the predictive value of tests by virtue of their application in populations with a higher incidence of disease. These are as follows:

Hepatic
Water & Acid Base
Cardiac Injury
Cardiac Evaluation
Hypertension
Renal
Cerebrovascular Accident (CVA)
Parathyroid
Pulmonary
Metabolic
Intestinal
Arthritis
Muscle
Pancreatic

I would like to comment on a few of these panels because of their specificity and usefulness.

CARDIAC INJURY - Creatinine Phosphokinase (CPK)
SGO Transaminase
Lactic Dehydrogenase

The cardiac injury panel has been enhanced with the addition of CPK and LDH isoenzymes where there are elevations of LDH and CPK in patients in the coronary care unit.

ARTHRITIS - E.S.R. Westergren
C-Reactive Protein
Antinuclear Antibody Titer
Rheumatoid Factor Slide Latex Test
Rheumatoid Factor Tube Latex Test
Titer @ 56°C
Titer @ 4°C
Uric Acid
Total Proteins
Electrophoresis
Albumin
$Alpha_1$ globulins
$Alpha_2$ globulins
Beta globulins
Gamma globulins

With acute joint inflammation, the sedimentation rate is elevated while the antinuclear antibody is elevated in almost all patients with lupus erythematosus. The rheumatoid factor, of course, is elevated in rheumatoid arthritis and uric acid is similarly elevated in gout.

METABOLIC - Glucose 2 hr. pc.----------Diabetes Mellitus
Uric Acid----------Gout and Hyperuricemia
Triglycerides and Cholesterol---Hyperlipoproteinemia
Creatinine----------Renal Function
Calcium----------Parathyroid and Bone Disease
Alkaline Phosphatase----------Liver and Bone Disease
SGO Transaminase----------Acute Liver Disease
Total Proteins and Albumin------Hyperproteinemia, e.g., Chronic Liver Disease and Multiple Myeloma

The metabolic panel reflects carbohydrate, lipid and protein metabolism in a comprehensive manner to make it a general screen for annual check-ups in adults.

HEPATIC - SGO Transaminase
Alkaline Phosphatase
Bilirubin Total
Bilirubin Direct
Prothrombin Time
Total Proteins
Albumin

In acute hepatic disease, a transaminase reveals the highest elevation with normal proteins. This is in contrast to chronic liver disease with depressed albumin, elevated globulins and depressed prothrombin but normal or only slightly elevated SGO transaminase. Alkaline phosphatase reflects interference with bile flow as does direct bilirubin in the obstructive phase of acute liver disease and also in chronic liver disease with obstruction.

In summary, there are few diseases which do not lend themselves to laboratory evaluation for early detection. However, the ultimate role of the laboratory in the early detection of disease can be enhanced in terms of cost effectiveness by careful selection of patient populations which have a higher incidence of disease in question. Moreover, an appreciation of sensitivity and specificity for each determination is important. We believe that the organ panel approach enhances the predictive value of positive measurements and examinations and, therefore, are more appropriate in the early detection of disease. However, we do not deny the utility of non-specific screening measurements with populations at large when there is a reasonable basis, i.e., age incidence, likelihood, or other reason for increased incidence.

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LABORATORY EMPLOYMENT IN AEROSPACE MEDICINE

Lt. Col. Prof. G. PAOLUCCI, IAF, MC
CENTROSERAEREO - SERVIZIO SANITARIO
Viale Università 4 - 00185 ROMA, It.

SUMMARY

This paper considers the main laboratory applications in Aerospace Medicine. Nowadays many techniques are usually employed, but others could be utilized in order to detect emotional changes in flight, and to evaluate tissue damage in traumatized subjects; the former by means of urinary catecholamine determination; the latter by the measurement of activity of some serum enzymes.

In addition to diagnostic fields, medical laboratory has applications in aviation accidents for identification of casualties, reconstruction of the bodies of traumatized persons, ascertainment of the vitality of lesions, toxicological examination, etc.

INTRODUCTION

The main laboratory applications in Aerospace Medicine can be summarized as follows :

1 - determination of the emo-biochemical state in normal or pathological conditions;
2 - detection of emotional changes in flight;
3 - evaluation of tissue damage in traumatized persons
4 - applications to aviation casualties.

1 - Determination of Emo-Biochemical State in Normal or Pathological Conditions

Emo-biochemical investigation in normal or pathological conditions, and values of laboratory techniques, are important and well known. Here it is only useful to outline the importance of the blood sedimentation (BS) and thromboelastography (TBE).

The BS technique is simple and useful and should be considered as a screening method of pathological survey.

The TBE is also a simple technique, useful for the ascertainment of blood coagulation; the knowledge of which is very important in aviators because they are exposed to traumas in aircraft mishaps; thromboelastography apparatus is necessary to carry out this test.

2 - Detection of Emotional Changes in Flight

Survey of in-flight emotions in air cadets is of great importance in the selection of flight personnel in order to prevent aviation accidents. Until now in-flight emotions could be ascertained only by post-flight interviews, but a young aviator is rarely disposed to admit his emotions or fears during flight; in such cases a modern laboratory may suggest whether an anxiety crisis take place (and even its degree), by means of urinary catecholamine essay, thus it is possible to inform flight instructors of cadet's emotions in flight.

The researches, carried out at the Aerospace Medical Center of the IAF showed that at the beginning of flight activity, in most student-pilots there is a psychic engagement, revealed by an increase of catecholamine excretion (25-30 mcg/h after flight missions against 3-5 mcg/h of normal values). This method which could be called "flight emotions detection" requires a fluorimeter.

3 - Evaluation of Gravity of Bodily Damage in Traumatized Persons

Long experimental and clinical studies, carried out by the author and others, have shown that tissue damage can cause an increase in the activity of some serum enzymes. The enzymes tested were GOT, GPT, LDH, MDH, ALKP, ACP, ALD. Although some of them increased after serious traumas, it was only the GOT which gave the constantly highest values between 24 and 48 hours after the trauma, lasting 2-3 days; in patients with fractures, values up to 5 times normal were registered. The analyses of enzymes permit the formulation of a prognosis even when there are no apparent lesions.

4 - Applications to Aviation Casualties

Analyses of the blood and other human biological remains are used in order to assign to a cadaver its own parts; histological and histochemical examinations are executed for diagnostic clarification; toxicological examinations determine alcohol, carbon monoxide or drug intake; identification methods are used for unknown victims; ascertainment of vitality is employed in order to establish whether a pilot died

during flight for natural causes, or after the flight as a result of trauma : the determination for the ascertainment of vitality varies with the kind of death (blood carbon monoxide determination in burns, plancton research in drowning, the examination of wounds in injuries).

CONCLUSIONS

The aim of this paper was to emphasize the importance of laboratory facilities in Aerospace Medicine and some of its applications. In my view, BS and TBE should be used routinely during fitness controls of flight personnel. Catecholamine determination and analyses of serum enzyme activity should be considered for possible utilization in the near future.

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COMMON PROBLEMS ENCOUNTERED IN LABORATORY SCREENING OF USAF FLIGHT CREWS FOR LATENT CORONARY ARTERY DISEASE

by

R. G. Troxler, Lt Colonel, USAF, MC, Chief, Clinical Pathology Branch
USAF School of Aerospace Medicine
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas 78235

SUMMARY

The worldwide epidemic of coronary artery disease in the technologically advanced nations has been well documented. Annual physicals in flying personnel could be easily altered to identify men at increased risk for coronary artery disease. Based on our correlations of lipid levels and coronary angiography, laboratory analysis of blood during the annual examination should include a determination of cholesterol and triglyceride levels. Quality control of the clinical laboratory is essential in multiphasic screening for coronary artery disease. The first step involves selection of a specific, accurate method, which compares favorably with the Abell-Kendall method. Accuracy and precision must be closely monitored by in-house and external quality control. Discrepancies must be carefully followed up so that analytic variability may be minimized. The clinician should be well aware of the possible extreme effects of biological variability on serum cholesterol levels. Biological variability contributes a significant percent of the total group variability which composes the normal range. The biological variability probably accounts for some of the overlap of cholesterol levels between patients with and without coronary artery disease. We present data showing that separation of diseased from nondiseased populations improves with increased laboratory precision. A normal range based on percentiles for 925 USAF male flyers without detectable coronary artery disease is presented. The limitations of this method of normal ranges are discussed.

INTRODUCTION

World Health Organization studies have shown that cardiovascular diseases were the major cause of death in 50 countries in all continents and accounted for 37% of all deaths in the world in 1967 (1). Between 1958 and 1968 there has been an alarming increase in mortality due to ischemic heart disease in males (2). Figure I shows the relationship of age to the development of atherosclerotic plaques in the left anterior descending coronary artery of males in a very large autopsy study of subjects from Czechoslovakia, Sweden, and the USSR (3). One can see that between ages 35 and 44, almost 90% of the males had significant coronary artery disease.

Figure II shows the rapid, almost exponential, increase in mortality due to coronary artery disease with age in U.S. males (4). Since personnel entering flying training are predominantly young males, the challenge of preventing coronary artery disease in aircrew members should be taken as a personal responsibility of the Squadron Flight Surgeon. The USAF residency training in Aerospace Medicine states as one of its objectives the early detection of problems affecting the health of aircrew members (5). Caris states "USAF studies have shown that the most common medical reason for permanent suspension of flyers from flying duties is coronary heart disease;" however, the usual history, physical, and resting EKG done in conjunction with the annual flying physical may fail to detect even advanced coronary artery disease prior to actual infarction (6).

In order to prevent coronary artery disease, some means other than the usual annual flying physical should be made to identify aircrewmen at increased risk of coronary artery disease. The three major or cardinal risk factors for coronary artery disease are hypercholesterolemia, cigarette smoking and hypertension (4). Of these three, only hypertension is assessed by the annual flying physical. Information on smoking could be easily included in the history form. Since blood is routinely drawn for hematocrit and VDRL, a serum cholesterol determination represents no extra discomfort to the patient. Since it has been shown that risk factors are additive (7), a cholesterol should be strongly considered in all flyers who smoke or demonstrate labile hypertension. These modifications of the usual annual flying physical have been proposed to the USAF Surgeon General by this division and are being seriously studied for future implementation.

SELECTION OF LABORATORY TESTS TO IDENTIFY PATIENTS AT INCREASED RISK FOR CORONARY ARTERY DISEASE

The early prospective studies in Framingham, Mass., USA, indicated that patients who ultimately died of coronary artery disease had higher levels of randomly drawn serum cholesterol, triglycerides, glucose and uric acid than controls (8). Salel et al. have determined by coronary angiography that serum triglyceride elevation is a predisposing factor in coronary artery disease in relatively young obese individuals (9).

We have evaluated serum cholesterol, triglyceride, phospholipids, 2-hour postprandial glucose, and uric acid in 200 consecutive patients undergoing coronary catheterization as part of their clinical evaluation at the United States Air Force School of Aerospace Medicine. The results are given in Table I.

TABLE I

RISK FACTORS IN RELATION TO POSITIVE AND NEGATIVE CORONARY ANGIOGRAPHY

Result of Angiography	Cholesterol	Triglyceride	Phospholipid	2-hour Postprandial Glucose	Uric Acid
Normals (Mean) N=120	226.85	118.54	238.61	106.01	6.455
Abnormals (Mean) N=80	251.65	164.62	256.32	105.73	6.507
Probability Means are from the same population	p <.001	<.025	<.025	N.S.	N.S.
Normals (S.D.)	38.69	63.47	50.96	27.34	10.12
Abnormals (S.D.)	20.73	154.53	48.25	30.12	14.30
Probability variance is from the same population	p <.001	p <.001	N.S.	N.S.	p <.001

Our statistical analyses show that the most significant difference between the two populations was found in serum cholesterol. These findings are in agreement with more recent epidemiologic data from the Framingham study. Cholesterol was found to be the most significant risk factor when statistical adjustments were made for concomitant triglyceride elevations. Kannel states that "risk of coronary heart disease in men can be estimated using any of the lipids evaluated; however, none proved more useful than an accurate total serum cholesterol" (10).

We have found that in our patient population the strongest correlations among lipids exist between cholesterol and phospholipids (r = .6). In view of the time and expense of phospholipids analyses, we do not recommend it for routine multiphasic screening. Lipoprotein phenotypes can be accurately estimated from cholesterol and triglyceride determinations and inspection of plasma refrigerated overnight. Since dietary treatment is based upon phenotypes, we recommend that serum triglycerides and cholesterols be determined in multiphasic laboratory screening for coronary artery disease. Triglyceride determinations are especially indicated in obese individuals, hypercholesterolemic patients, and patients with glucose intolerance.

QUALITY CONTROL OF CLINICAL LABORATORY RESULTS

The following general discussion is applicable to all lipid determination. Cholesterol is chosen because it is a cardinal risk factor.

Clinical laboratory data were previously useful only in confirming physicians' suspicions of the presence of clinical disease. Discrepancies in accuracy and precision were tolerated since patients were sick whether their SGOT was 1000 or 4000. The phrase "close enough for clinical purposes" was commonly used to distinguish clinical laboratory results from research laboratory data.

Poor accuracy or precision in a clinical laboratory engaged in multiphasic health testing cannot be tolerated. The effects are inaccurate normal ranges, the additional expense of followup of spuriously elevated results in normal patients, the inaccurate prediction of the true risk of coronary artery disease in the population being screened, and the inability to properly evaluate the success or failure of the risk factor modification program.

Figure III is an estimate of the decreased risk of coronary artery disease as a result of lowering the serum cholesterol based on prospective epidemiologic data (4). One can see that a 10% decrease in serum cholesterol might result in a 25% decrease in the risk of coronary artery disease.

Tonks surveyed 170 clinical chemistry laboratories in Canada in the 1950's and found that 39-48% of reported cholesterol values were inaccurate by a value greater than 10%, depending upon the method the laboratory used (11). The cholesterol results were considerably higher than the true values and most of the methods lacked specificity. The Schoenheimer-Sperry modification of the Liebermann-Burchard reaction gave the most accurate values. Ferric chloride methods ran a reasonably close second. Schwartz and Hill, in their review of the problems of interpreting serum cholesterol values, indicate that difficulties in performance of cholesterol analyses are worldwide (12). In a 1971 letter to the editor, the Chairman of the Department of Laboratory Medicine at Yale University School of Medicine states: "I believe that more than 90% of cholesterol values currently issued to physicians are unsuitable for the practice of medicine or for clinical research" (13). Schwartz and Hill state that the main reasons for these difficulties are differences in cholesterol methods and the lack of true standards for cholesterol analysis.

Before an accurate result can be obtained on a serum cholesterol determination, a specific method must be chosen. A test is not specific if it is significantly affected by substances other than the constituent it was designed to measure. Substances such as carotene and vitamin A interfere with cholesterol analysis. The interferences are often method dependent. Cholesterol is present in the serum in the free

and esterified form. The Liebermann-Burchard method develops more color with cholesterol esters than with free cholesterol while the reverse is true with the direct ferric chloride methods. Serum bilirubin elevations and lipemia also cause interference with the direct ferric chloride method.

The most accurate and precise method for serum cholesterol is the Abell-Kendall method. This method converts all cholesterol esters to free cholesterol by hydrolysis. The free cholesterol is extracted from the serum by petroleum ether and color is developed by the Liebermann-Burchard reaction (14). Automated methods are required for usual multiphasic health screening. Good correlations with the Abell procedure are obtained when isopropanol extracts of serum are analyzed by the AutoAnalyzer II method (15). Tonks has reviewed cholesterol methodology and recommends the AutoAnalyzer II method for routine automated cholesterol determinations in the clinical laboratory (16). A similar method is currently used in our laboratory.

The lack of a true cholesterol standard imposes a great burden on the clinical laboratory. One alternative is a high purity standard (99.7 ± 0.2%) available from the U.S. National Bureau of Standards (NBS). However, we have no guarantee that an isopropanol extract of this pure cholesterol standard will react exactly like the extract of the lipoprotein that normally carries the cholesterol in the bloodstream. A true cholesterol standard is a sample of serum that has been analyzed by the NBS, the U.S. National Reference Laboratory. Many clinical laboratories use commercially available sera with "assayed values." Witter et al. studied 12 commercially available reference sera by the Abell reference method and found the stated values were inaccurate in 6 (50%). The authors correctly concluded that commercial serum standards should not be the sole means of calibration of methods for serum cholesterol (17). Since the accuracy of a laboratory value is defined as the closeness of the result to the true value and since only a true cholesterol standard could determine where the true value is, the problem of accuracy in the clinical laboratory at first seems insoluble.

However, alternatives other than defining accuracy by true cholesterol standards exist. They are time consuming, tedious, and somewhat expensive, but absolutely essential for maintaining accuracy in the clinical laboratory. One alternative involves recovery studies. In recovery studies, increasing amounts of pure cholesterol standard can be added to serum. The results, plotted on graph paper, should be linear. Discrepancies in the amount added versus the amount recovered may be useful in identifying losses of cholesterol due to the extraction phase of the procedure. The chemical reaction phase of the method may be monitored separately from the extraction phase by the analysis of increasing concentrations of a pure cholesterol standard dissolved in the solvent normally used in the procedure. The optical absorbance of the color developed plotted against the concentration of the cholesterol standard should be linear.

Clinical laboratories have quality control programs which primarily measure precision. While precision never implies accuracy, it is an essential prerequisite. Precision is usually monitored by duplicate daily analyses (within day precision) and replicate analyses over a period of months (day to day precision) of sample portions of a large quantity of serum. The degree of precision is judged by how close the results are to each other. Precision is increased by greater attention to technical detail and by automating manual procedures. It is adversely affected by changing personnel, changing instruments, deterioration of reagents, and mechanical or electronic failures of laboratory instruments. The degree of precision required for cholesterol analyses should be 10% or less (11). A standard method of evaluation of clinical laboratory precision is the relative standard deviation or the coefficient of variation. It is defined as the standard deviation divided by the mean, multiplied by 100 and expressed as a percent. Schwartz and Hill state that an acceptable coefficient of variation (C.V.) for routine cholesterol analyses is 3%. The Abell method should have a C.V. of 1.5% (12).

The usual assessment of accuracy done in a routine clinical laboratory is by regional laboratory proficiency surveys. These surveys send a sample of lyophilized serum to a number of reference laboratories of recognized competence. The sample is then sent to all subscribers to the survey program. The results sent to the participants compare their results to those of the reference laboratory and to those of other participants in the survey. Good results on these surveys do not always insure accuracy of routine specimens because the survey samples are usually given special treatment. However, consistently poor or biased results on any single determination, such as a cholesterol determination, does indicate that in all probability routine cholesterol determinations are inaccurate.

In summary, accurate results must start with a specific method which correlates well with the Abell-Kendall method. High purity standards must be used to calibrate the methods. Precision must be closely monitored. The laboratory should participate in a proficiency survey program. All consistent discrepancies found by the survey should be followed up by recovery studies with high purity standards to reassess the accuracy of the procedure.

BIOLOGICAL VARIABILITY

Problems with interpretation of serum lipid data, and in particular cholesterol, are further compounded by significant biological variations. When a series of determinations for serum cholesterol are performed on a single individual over a period of time, the results will be found to vary about a central point. If the variability due to the analytical procedure is monitored during this same time period, the total variation of the measurement minus the variation due to the laboratory method represents the biological variation of the serum cholesterol. In other words, Total Variation of Each Individual's Measurement = Laboratory Variation + Biological Variation. The biological variation of cholesterol is extremely important because this variability contributes a significant percent of the total group variability, which in turn is the normal range for that group.

Too few studies on the normal range of serum cholesterol consider the analytic-variation. But analytic variability, if large enough, could artifactually widen the distribution of cholesterol values of a group of normal individuals and blur the zone of demarcation between patients with and without coronary artery disease.

Williams, Harris, and Cotlove et al. in a series of articles compared the biological and analytical variability of cholesterol and found that when 68 individuals were sampled weekly for 3 months, the biological variation averaged 62% of the total variation, therefore the lab variation was 38%. The coefficient of variation of the analytical procedure, averaged over three months, was 3.0%. They cite references stating that if the analytical variation is not 50% or less than the total variation, serious artifacts are introduced into the range of variation of a group of normal individuals, i.e., the normal range (18). There is general agreement in the literature on this with figures ranging from 20% to 50% (19).

Williams et al. compared the variation of each individual's cholesterol to the variation of the cholesterol of the whole group. They state that a cholesterol value could significantly rank a person within "normal population" only if the combination of individual (personal) variation and the laboratory variation was significantly less than the total between individual variability of the group (18). Further increasing the precision should theoretically allow greater separation between diseased and nondiseased groups of patients. Fleischman et al. studied the precision of total cholesterol analysis compared to the precision of the extraction procedure. They found that the laboratory variation due to the manual extraction procedure was almost as large as the variation due to the automated chemical reaction (20). Wease et al. working in our laboratory have automated the extraction step and greatly reduced this imprecision (21). Table II illustrates the effects of increasing laboratory precision on the ability of the level of serum cholesterol to discriminate between normals and a population with coronary artery disease.

TABLE II

EFFECT OF INCREASED PRECISION ON CHANGE IN MEAN SERUM CHOLESTEROL

BETWEEN DISEASED AND NONDISEASED INDIVIDUALS

Years	Diagnosis	N	Mean Serum Cholesterol mg/dl	Avg. C.V.
Group I				
1966-70	CHD	66	224	5.4
1966-70	Normal	300	218	5.4
			6†	
Group II				
1971-72	CHD*	80	252	4.5
1971-72	Normal*	120	227	4.5
			25†	
Group III				
1973-74	CHD severe*	25	276	2.1
1973-74	CHD mild*	14	241	2.1
1973-74	Normal*	38	224	2.1
			52†	

* confirmed by coronary angiography

† difference between largest and smallest number in column.

Differences between groups I and II showing the poor discriminating power of a serum cholesterol in group I are partially related to the imprecision of the laboratory and partially related to the method of diagnosis of CHD. Not all of the abnormal patients in group I had coronary angiography and some were evaluated after myocardial infarction. Lipid values measured after myocardial infarction are not as consistently related to the severity of coronary artery disease (22). Differences between groups II and III reflect increased laboratory precision and the subclassification of coronary artery disease. One can see from the data in group III that the average level of serum cholesterol does increase with the severity of coronary artery disease.

However, even with clearly demarcated disease groups and adequate precision, the data suggest considerable overlap of cholesterol levels between subjects who have coronary artery disease and those who are angiographically negative. One possible explanation is that the biological variation of the individuals

within the group is not homogeneous and that some "normal" individuals actually vary from the lower to the upper portion of the "normal range" on successive determinations. In our patients, repeat cholesterols sometimes vary as much as 80-100 mg/dl, but the variation differs widely between individuals.

It is well known that many factors affect the individual biological variation of serum cholesterol, such as age, diet, weight, height, sex, genetics, social class, cigarette smoking, the season of the year, geographical regions, blood groups, and mental stress (12,23,24). Genetic hypercholesterolemia actually affects only 1 out of every 500 individuals or .1% of the population (25). In multiphasic screening of 5,799 males and females 50 years old and over from various ethnic groups, Bunow found 3.08 to 12.55% of them had cholesterols greater than 300 mg/dl (26). Other studies have stressed that the environment has a greater effect than ethnic background on the level of serum cholesterol. Reisel has reviewed the relationship between hypercholesterolemia and atherosclerosis and found that the mean serum cholesterol of various countries is related to the percent of total calories due to fat in their diet (27).

Van Houte and Kesteloot studied serum cholesterol in 12,532 members of the Belgian Army (23). They found serum cholesterol increases rapidly between ages 17 and 35 years; then progressively more slowly until age 45. They found 75% of the total increase in serum cholesterol occurring between 17 and 60 years occurred below the age of 35.

In all age groups cholesterol increased with weight, especially in younger age groups. Cholesterol levels were inversely related to height and higher in blood group A individuals. Serum cholesterol increased with rank, physical inactivity, and smoking 20 cigarettes per day. Pincherle's survey (24) of the serum cholesterol in 7,133 London businessmen agreed with the findings of Van Houte and Kesteloot (23). In addition, they found positive correlations between elevated serum cholesterol and systolic blood pressure, elevated serum uric acid levels, and the cold months of the year. We have noted similar seasonal variations in our patients.

Of all the factors affecting the individual biological variation of serum cholesterol, we find mental stress the most difficult to measure. Wertlake et al. studied 44 male medical students during a week of examinations and during periods when they were free of examinations. Mean cholesterol levels increased 11% during the examinations. Students varied in their lability of cholesterol; 55% varied 15 mg/dl or less. In 45% of the students the cholesterol levels seemed especially labile, showing an increase of 16 mg/dl or more. In one individual cholesterol increased from 259 mg/dl to 536 mg/dl (28). Peterson et al. compared 5 students with labile cholesterols to 5 with stable cholesterols. They found that cholesterols in the labile group were higher and varied more widely from hour to hour than the stable group. While cholesterols in the labile group generally increased from 90 to 100 mg/dl following a mental annoyance, and 60 to 80 mg/dl following a subcutaneous injection of epinephrine, no such consistent response was found in those individuals with stable cholesterol levels (29). In a further study of students with labile serum cholesterols, Peterson found even the anticipation of a physical stress elevated serum cholesterol from 20 to 80 mg/dl with a maximum increase 2 to 3 hours after announcement of the stress (30).

Repeat cholesterols on 132 USAF repatriated prisoners of war decreased in 113, increased in 18, and remained unchanged in only 1. Statistical analysis using the sign test shows this cannot be due to chance ($p < .001$). Patients seen at our evaluation center have often told us they feel threatened by our clinical evaluation. In a study of 77 patients undergoing coronary angiography as part of their clinical evaluation we found significant correlations between serum cortisol and serum cholesterol ($p < .001$) (31).

NORMAL RANGE OF SERUM CHOLESTEROL

Amador, in a review of the methods of establishing a normal range, has set up several criteria which must be fulfilled before a normal range can be useful in diagnosis. 1) It must have been determined in healthy subjects, 2) it must have been determined with the same method employed to study patients, 3) biological variations such as age, sex, race, pregnancy, time of day, food, and season of the year should have been looked for (32). From the preceding discussion, we could also add that the precision of the test must be such that it does not artifactually widen the normal range. But above all, for maximum diagnostic utilization, the test values should clearly separate a diseased from a nondiseased population.

The cholesterol values obtained from patients in group II of table II appear to overlap. Table III is an expansion of that data classed in 10 mg/dl intervals. The mean and range are from the original data.

TABLE III

FURTHER STATISTICAL ANALYSIS OF GROUP II FROM TABLE II

	N	Mean	S.D.	Median	Mode	Range
Normals†	120	226.8*	38.69	220-229*	240-249*	112-330*
Abnormals†	80	251.6*	20.73	240-249*	240-249*	169-392*

* Serum cholesterol in mg/dl.

† Established by coronary angiography.

The theoretical normal range (mean ± 2 S.D.) for the normal group is 149 mg/dl to 304 mg/dl. The data from U.S. prospective studies indicate that patients with a serum cholesterol exceeding 200 mg/dl are at increased risk of coronary artery disease and deserve a medical evaluation (33).

Figure IV shows that patients whose serum cholesterol was 250-274 mg/dl had approximately twice the risk of developing coronary thrombosis as patients with serum levels of 225-249 mg/dl (4). These data clearly indicate that the usual method of interpreting normal ranges based upon a Gaussian distribution cannot be applied to serum cholesterol due to its lack of specificity. Serum cholesterol does not clearly separate normal from abnormal individuals. Unfortunately, while no such single blood test has been found specific for coronary artery disease, a random serum cholesterol has been shown to be the best single indicator of risk from coronary artery disease (10).

Wynder and Hill surveyed the opinions of 35 leading investigators in the field of atherosclerosis as to the ideal level of serum cholesterol in males (34). The average of their responses for males is as follows:

Age 10-146 mg/dl
Age 30-174 mg/dl
Age 50-185 mg/dl

It is obvious from our data that not every patient with a cholesterol over 185 mg/dl has demonstrable coronary artery disease. Ideal cholesterol values are standards against which we measure our everyday values. What is needed is a simple estimate of the chance or probability that a patient belongs to the nondiseased (coronary arteries angiographically negative) population.

Herrera's method of establishing percentiles on a normal population should suffice for this purpose (35). She states the sample size should include at least 40 subjects and chose 2.5 and 97.5 percentiles as the normal range. The percentile method is not invalidated by nongaussian distributions of the population.

The following percentile distribution is based upon a population consisting of 925 USAF aircrew members who had previously had annual physical examinations. They were evaluated by the USAF School of Aerospace Medicine from Jan 1967 to Dec 1969. Their cardiovascular evaluation consisted of a routine physical examination with multiphasic laboratory screening, resting electrocardiogram (ECG), vector cardiogram, and ECG monitoring in conjunction with exercise stress testing on a treadmill. No detectable evidence of coronary artery disease was found in any of these patients.

The method for determining cholesterol was by manual silicic acid extraction (36). Color was developed by anhydrous ferric chloride-glacial acetic acid-sulfuric acid (37). The standard deviation of the method averaged 4.6 mg/dl and the C.V. 3.36, during the three-year period. The numbers in each group are 53, 203, 231, 186, 90, 123, and 36 for age groups 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and 50+ respectively. The age group 50+ has 36 instead of the 40 required by Herrera's method of percentiles.

Biological variability, in addition to age and sex, is accounted for in that all subjects were drawn between 0730 and 0830 and were advised to eat a 300 gm carbohydrate diet for three days prior to their clinical evaluation. The cholesterol levels all represent initial day values. When repeat cholesterols on 44 patients were ordered by the clinical staff, the majority of the repeat values were lower than the initial values. (54% decreased by 10 mg/dl or more.) The percentile chart is based upon single initial values because of expediency and because single cholesterols were found useful in the epidemiological studies in Framingham, Mass., USA. Clark et al. have found that in a group of 109 males whose serum cholesterols were followed biannually for 18 years, subjects who began in the highest decile in general remained in the highest quartile (38).

The inherent biological variability of cholesterol makes an estimate of the patient's percentile from a single cholesterol determination hazardous. We recommend at least three cholesterol determinations for a true estimate of the patient's percentile; others recommend 5 (39). Repeat cholesterols will also give the physician an idea as to whether the patient belongs in the "cholesterol labile" or "cholesterol stable" category. Factors which affect biological variability such as physical inactivity, season of the year, weight, and mental stress must all be kept in mind when evaluating the effectiveness of prescribed cholesterol lowering regimens.

The cholesterol values by percentile of 924 normal males are given in Table IV.

TABLE IV

PERCENTILE DISTRIBUTION OF CHOLESTEROL VALUES

Serum Cholesterol mg %	Age Group 20-24	25-29	30-34	35-39	40-44	45-49	50 +
110	0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.02
115	0.01	< 0.01	0.01	< 0.01	< 0.01	< 0.01	< 0.02
120	0.01	< 0.01	0.01	< 0.01	0.01	< 0.01	< 0.02
125	0.03	< 0.01	0.02	< 0.01	0.01	< 0.01	< 0.02
130	0.03	0.01	0.02	0.01	0.01	< 0.01	< 0.02
135	0.05	0.02	0.03	0.01	0.01	0.01	< 0.02
140	0.09	0.04	0.03	0.02	0.02	0.01	< 0.02
145	0.13	0.08	0.04	0.03	0.02	0.01	0.02
150	0.17	0.11	0.07	0.05	0.02	0.01	0.02
155	0.18	0.14	0.08	0.10	0.04	0.04	0.02
160	0.24	0.19	0.16	0.15	0.06	0.06	0.05
165	0.30	0.23	0.19	0.17	0.08	0.07	0.08
170	0.37	0.28	0.23	0.21	0.11	0.10	0.11
175	0.41	0.32	0.29	0.24	0.13	0.12	0.11
180	0.50	0.41	0.35	0.29	0.18	0.13	0.19
185	0.62	0.47	0.41	0.34	0.21	0.16	0.19
190	0.71	0.53	0.47	0.43	0.33	0.25	0.27
195	0.75	0.58	0.52	0.51	0.34	0.27	0.27
200	0.77	0.62	0.59	0.58	0.44	0.32	0.41
205	0.79	0.68	0.64	0.62	0.52	0.36	0.44
210	0.83	0.72	0.68	0.68	0.58	0.45	0.47
215	0.83	0.78	0.72	0.70	0.63	0.50	0.47
220	0.84	0.83	0.76	0.75	0.64	0.52	0.47
225	0.86	0.85	0.77	0.77	0.65	0.59	0.52
230	0.88	0.91	0.82	0.80	0.71	0.64	0.52
235	0.88	0.93	0.86	0.83	0.71	0.66	0.58
240	0.88	0.94	0.90	0.87	0.71	0.73	0.63
245	0.90	0.94	0.91	0.87	0.73	0.76	0.69
250	0.92	0.95	0.93	0.88	0.82	0.78	0.74
255	0.96	0.96	0.93	0.89	0.85	0.82	0.77
260	0.98	0.97	0.94	0.91	0.92	0.82	0.77
265	0.98	0.97	0.96	0.92	0.94	0.85	0.77
270	0.98	0.97	0.96	0.93	0.95	0.90	0.86
275	0.98	0.98	0.97	0.94	0.95	0.91	0.88
280	0.98	0.98	0.97	0.95	0.97	0.93	0.94
285	0.98	0.98	0.99	0.97	0.97	0.94	0.97
290	0.98	0.99	> 0.99	0.97	0.97	0.96	0.99
295	0.98	> 0.99	> 0.99	0.97	0.98	0.96	> 0.99
300	0.98	> 0.99	> 0.99	0.97	0.99	0.97	> 0.99
305	0.98	> 0.99	> 0.99	0.98	> 0.99	0.98	> 0.99
310	0.98	> 0.99	> 0.99	0.98	> 0.99	0.98	> 0.99
315	0.98	> 0.99	> 0.99	0.99	> 0.99	> 0.99	> 0.99
320	0.99	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99

The interpretation of cholesterol of 250 mg/dl in an individual patient who is 25 years of age is: The patient's cholesterol level is higher than 95% of males without detectable coronary artery disease in his age group.

CONCLUSION AND RECOMMENDATIONS

Periodic monitoring of serum cholesterol in young males may prevent the present epidemic of coronary artery disease. Problems in the interpretation of serum cholesterols involve obtaining a specific, accurate, method by comparing it to the Abell method, controlling analytical variation, and being aware of biological variation. Finally, the question of "What is a normal serum cholesterol?" will go unanswered until a more specific blood or serum test for coronary artery disease is found. The considerable overlap in cholesterol levels between patients with and without documented coronary artery disease should encourage the search for new risk factors and the use of multivariant analysis of known risk factors to identify that population at greatest risk for coronary thrombosis.

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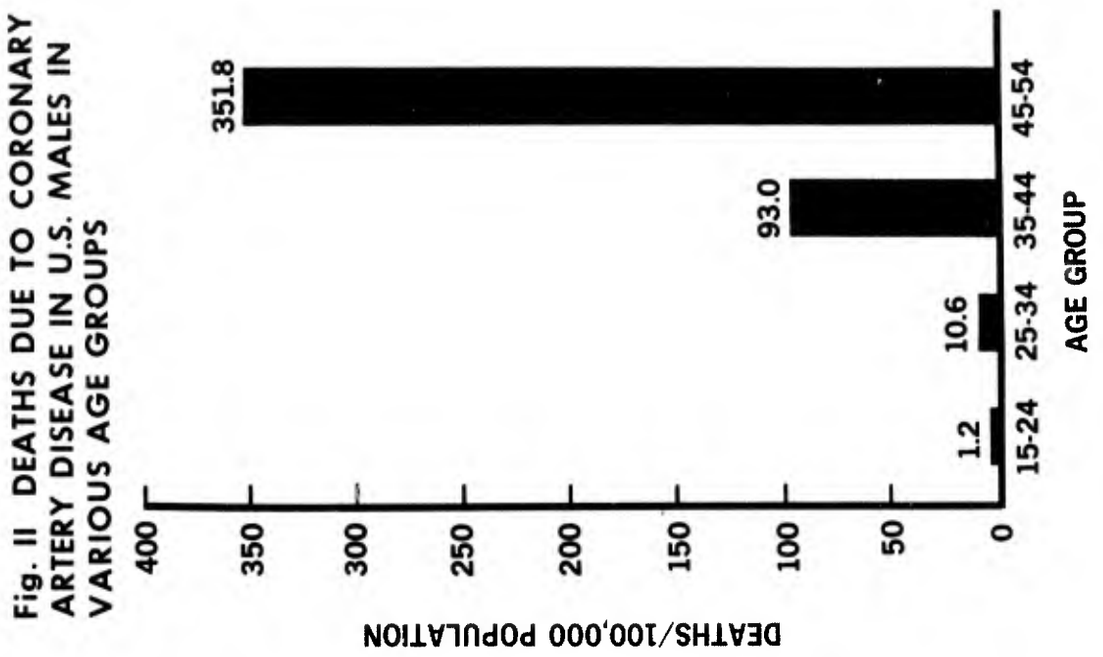


Fig. II DEATHS DUE TO CORONARY ARTERY DISEASE IN U.S. MALES IN VARIOUS AGE GROUPS

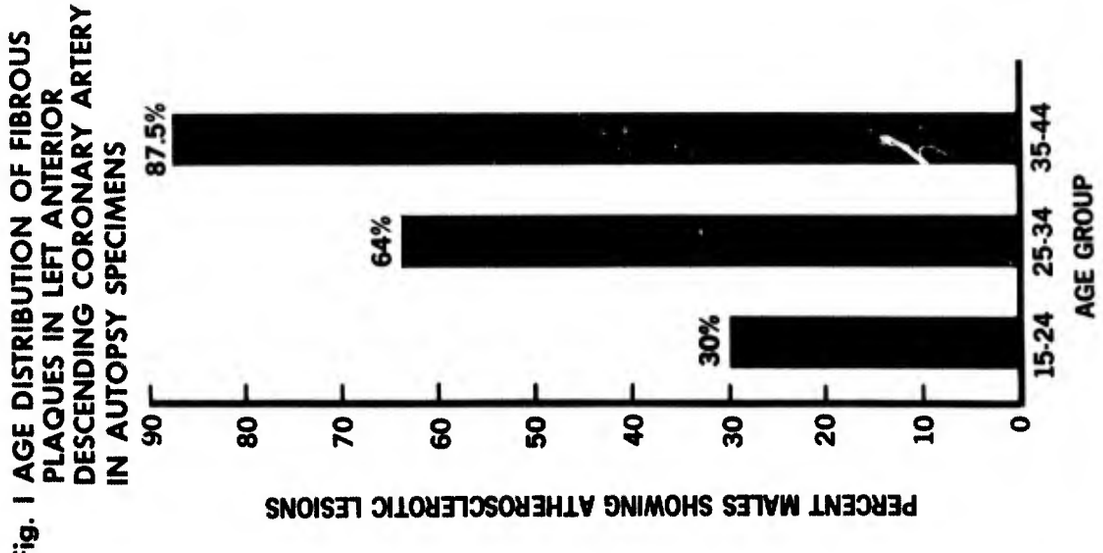


Fig. I AGE DISTRIBUTION OF FIBROUS PLAQUES IN LEFT ANTERIOR DESCENDING CORONARY ARTERY IN AUTOPSY SPECIMENS

Fig. III RELATIONSHIP OF RESULT OF LOWERING SERUM CHOLESTEROL AND ESTIMATED DECREASE IN CORONARY ARTERY DISEASE

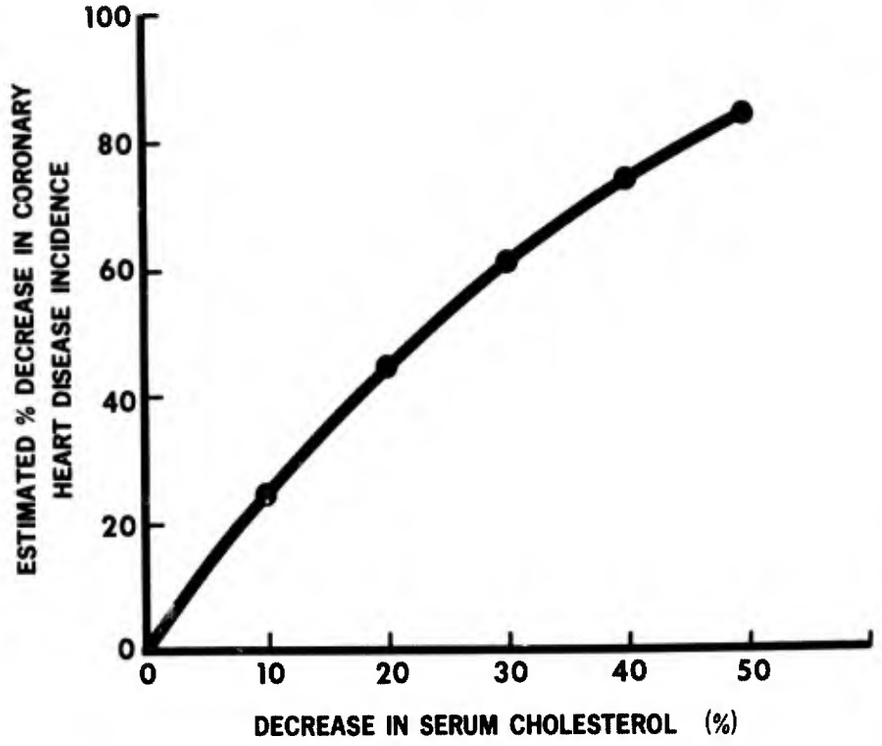
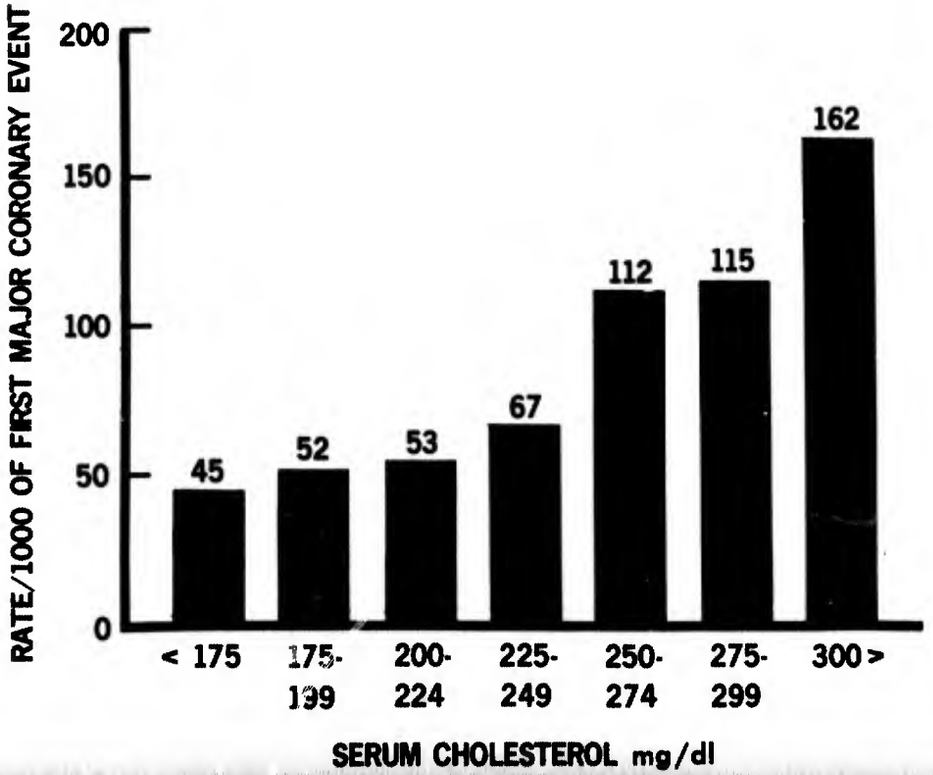


Fig.IV RATE OF CORONARY ARTERY DISEASE AS RELATED TO LEVEL OF SERUM CHOLESTEROL



EPIDEMIOLOGICAL STUDIES OF SUBCLINICAL DIABETES MELLITUS

by

K. REICHENBACH-KLINKE, Maj, MD, GAF
German Air Force Institute of Aviation Medicine
Fürstenfeldbruck

A clinically manifest diabetes mellitus disqualifies for the job of a pilot. This may also apply to subclinical diabetes. The great incidence of this disease was demonstrated in numerous screening-test-studies of glucosuria the world over (summary in 1). Most authors supposed an incidence of 1 or 2 percent of the population. Some few authors using Glucose-tolerance-tests estimated an incidence of 2-17%(2) and 12-14%(3).

In our institute we try to get an early diagnosis because of this great incidence and the aeromedical relevance. For this purpose the division of diabetes mellitus by the WHO expert commission of 1965 (4) into 4 states is useful. Its nomenclature was used by us:

I. Potential diabetes: Healthy persons with hereditary disposition.

II. Latent diabetes: Persons whose GTT was abnormal only while under some stress, or when obese. The cortisone - augmented GTT is abnormal.

III. Asymptomatic, subclinical or chemical diabetes: Persons with an abnormal GTT.

IV. Clinical diabetes: Persons with an abnormal GTT and symptoms of diabetes.

Only state III, subclinical diabetes, was of relevance to our study, because we expected these findings in a number of cases. In the following we have studied the incidence of this form of diabetes in pilots and in pilot applicants. We also tried to find a coincidence of other biochemical data: of liver and risk-factors of coronary-disease (cholesterol, triglycerides, uric-acid), with due regard to hypertonia, obesity, and ECG.

METHODS:
For the determination of glucose we used blood from the capillaries of the finger-tips. This technique causes values of better reproducibility than venous blood, because the glucose-level in capillaries is nearly that of arteries (5). The capillary-venous difference during a GTT is said to be 40% (6). Immediately after taking the 100 µl blood it was put into perchloric acid for deproteinisation. The glucose was determined in the supernatant by hexokinase. Controlling the precision from day to day mostly results in a monthly variation-coefficient between 1 and 2%.
Before 1971 blood glucose was only determined in the fasting pilot. Since the end of 1971 until 1974 pilots were examined as to their carbohydrate-metabolism: First the blood sugar of the fasting pilot was determined. It was established once more 90 minutes after drinking 100 g glucose in 400 ml water, after alcohol abstinence and three days high-caloric alimentation. All pilots, whose blood-glucose-values were higher than 135 mg/ 100 ml 90 minutes after treatment with 100 g glucose, were once more examined the following day with a SGTT or tolbutamide test. The pathological findings were once more verified stationary for therapy.
For a statistical study we used the results of the years 1972 and 1973 in 3792 test subjects.

Since October 1974 we have been using another procedure: Blood sugar was first determined in fasting pilots, then 60 minutes and 120 minutes after treatment with 100 g glucose. In addition each one was tested for glucosuria before and after the test with clinistix.
The following criteria applied for test evaluation (according to Ref. 7 and Ref. 4):

fasting:	Normal:	less than 120 mg/100 ml
After 1 hour:	Normal:	less than 160 mg/100 ml
	Borderline:	160-180 mg/100 ml
	Abnormal:	more than 180 mg/100 ml
After 2 hours:	Normal:	less than 120 mg/100 ml
	Borderline:	120-140 mg/100 ml
	Abnormal:	more than 140 mg/100 ml

If one value was abnormal, carbohydrate intolerance was suspected. For our statistics we used the results found in 1440 subjects.
In the serum of the examinees we determined: cholesterol (method of LIEBERMANN-BURCHARD), triglycerides (enzymatic determination of glycerine after saponication with potassium hydroxyde), uric-acid (enzymatic with uricase), bilirubin (with sulphanilic-acid and sodium-nitrite), SGOT and SGPT (substrate-optimized in the colorimetric UV-test), and Gamma-GT (with gamma-glutamyl-p-nitrinalid and glycil-glycine as substrate). Limits for normal values were: Cholesterol 260 mg / 100 ml ($\bar{x}+2s$), and triglycerides 170 mg / 100 ml, based on a statistical evaluation of our values, bilirubin 1 mg / 100 ml uric-acid 7 mg / 100 ml (8). The limits of SGOT and SGPT were calculated individually according to age, height, and weight in line with a study of LAUDAHN (9). Gamma-GT according to SZASZ (10): 28 U/l.

RESULTS:

1. Normal distribution of blood glucose values of the fasting test person is slightly asymmetric. In 1972, for example, we found:

n	1967
$\bar{x}$	86,25 mg/100 ml
s	11,22 mg/100 ml
v	0,130
$n_{(\bar{x}+s)}$	534
$n_{(\bar{x}-s)}$	688
$n_{(\bar{x}+s)}$	725
$n_{(\bar{x}-s)}$	894
$n_{(\bar{x}+s)}$	760
$n_{(\bar{x}-s)}$	923

Our study covering the year 1970 concerning fasting blood-glucose and overweight-population shows no difference in the normal distribution of blood glucose-values relative to normal-weight persons. 90 minutes after a load with 100 g glucose we registered the following distribution of values:

	1972	1973
n	1697	2095
$\bar{x}$	103,77	104,73 mg / 100 ml
s	24,48	20,30 mg/100 ml
v	0,235	0,193
$n_{(\bar{x}+s)}$	582	680
$n_{(\bar{x}-s)}$	730	847
$n_{(\bar{x}+s)}$	718	887
$n_{(\bar{x}-s)}$	913	1098
$n_{(\bar{x}+s)}$	747	935
$n_{(\bar{x}-s)}$	918	1113

2. RESULTS OF DIABETES-DIAGNOSES 1972/73

The results of GTT-screening 90 minutes after 100 g glucose are shown in the following table:

Group 1: After tolbutamide-test or SGTT for 3 hours on the next morning no indication of glucose intolerance.

Group 2: Next morning tolbutamide-test or SGTT was abnormal, but was not reproduced in the hospital at home some weeks later.

Group 3: Next morning tolbutamide-test or SGTT was abnormal and reproduced in the home town hospital.

Group 4: Not further examined.

Glucose-Level 90 min. after 100 mg/100 ml	Number of Cases	Group 1	2	3	4
136 - 140	24	15	5	0	4
141 - 145	35	20	4	7	4
				20%	
146 - 150	17	7	3	4	3
				24%	
151 - 155	15	10	3	2	0
				13%	
156 - 160	13	11	0	2	0
				15%	
more than 160	40	12	10	13	5
				33%	
TOTAL	144	75	25	28	16
				19%	

3,8% of the pilots showed blood-glucose values higher than 135 mg / 100 ml 90 minutes after one treatment with glucose. 0.74% were diagnosed clinically as suffering from subclinical diabetes. It is shown, that our pre-diagnosis was reproduced in 53% in the home-town hospital.

3. RESULTS OF THE DIABETES-DIAGNOSES FROM OCTOBER 1974 UNTIL FEBRUARY 1975:

According to the previously described criteria 10% (144 from 1440) showed an abnormal GTT. Other pathological findings of abnormal GTT were as follows:

	Abnormal GTT	Normal GTT
Elevated bilirubin, SGPT, Gamma-GT:	30%	3,3%
Hypertriglyceridemia	28%	17,2%
Elevated cholesterol	9%	3,2%
Hyperuricemia:	25%	11,6%
Overweight	18%	
Hypertonus	15%	
ECG: Light Alterations in s-t after exercise	2%	

In the following table the findings are reduced to the level of single measures of GTT.

	Elevated Glucose in Blood in SGTT					
	Fasting	1h	2h	Fasting +1hrs	Fasting +2hrs	1hr+2hrs.
	0 0%	41 28%	9 6%	0 0%	1 0,7%	93 65%
Glucosuria after test	-	11	1	0	1	13
Abnormal in Liver	-	10	2	-	-	31
Elevated Cholest. or (and) Triglyceride	-	5	2	-	-	39
Hyperuricemia	-	7	2	-	-	27

DISCUSSION:

Assuming that SGTT is the determining factor for the diagnosis of diabetes, we have to reckon with a frequency of 10% in our pilots, according to our results. The reproducibility of the SGTT is said to be very bad (about 50%, 11). We also often found, that our SGTT could not be reproduced some weeks later. But since even an abnormal SGTT is not reproducible, we have to first estimate state II of diabetes. Mostly it cannot be decided for sure, whether it is state II or the insuffi- ency of the method. Disclosing the diagnosis of diabetes to a pilot may be problematical, if he feels without complaints. In a long-term study we shall deal with this question in detail later on. Other pathological findings in coincidence with an abnormal SGTT may be useful for a diagnosis. In our findings it is of high interest, that also in subclinical cases a much greater number of elevated liver encymes and lipids in serum is measured, than in normals. It seems to be of no importance whether one or more measurements in the SGT. are elevated. In our subjects the coincidence of abnormal SGTT to pathological findings of the liver is most evident. It is stated that 78% of diabetes have a fatty liver (12). Only in two of our test persons did we find a histological diagnosis of punctate: It was fatty liver.

Initially we used only the measurement of fasting and one value after 100 g glucose oral. Very few examinees were found to have diabetes. A measurement of fasting blood glucose seems to be without importance, When screening the GTT there are only two measurements of consequence after oral administrat. of glucose. Even though it may be impossible to obtain a safe diagnosis in a pilot, because of an abnormal GTT which is not reproducible, it is necessary to devote attention to him. For example, once a pilot was found to have a slightly elevated 90-min-value in GTT. The tolbutamide test was normal, as was uric-acid, triglycerides and SGPT. There were no internal findings, and no hereditary risks of diabetes, but in the USA he one day noticed an abrupt alteration in visual acuity, after having suffered from polyuria and polydipsia accompanied by intermittent indisposition some 2 or 3 weeks earlier. He was found to have had a manifest diabetes mellitus and he was given insulin treatment.

Pointing out the limits of laboratory tests, each pilot should be informed in detail about the subjective symptoms of manifest diabetes. He should also be convinced about the possible damages, if he keeps this knowledge from the flight surgeon.

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Radioimmunoassays – New Laboratory Methods in Clinic and Research

E.H. Graul and H. Müller
Clinic and Policlinic for Nuclear Medicine
University of Marburg
355 Marburg/Lahn
Lahnstrasse 4a
West Germany

Summary

Radioimmunoassays (RIA's) permit quantitative determination of serum components, especially hormones and immunoglobulins, such as IgE, in very slight concentrations. Pharmaceuticals, such as digitalis, can likewise be measured, thus providing a better check on therapy.

RIA's are *in vitro* tests which do not expose the patient to radiation. They are based on the antigen-antibody reaction, in which the substance to be measured and the corresponding radioactively labelled substance compete for binding sites on the specific antibody. Certain complete RIA's are already available commercially. The Australia RIA is highly sensitive and specific, as was confirmed by an examination of sera from over 2000 blood donors.

Various RIA's can, however, yield divergent results on serum from the same patient, as was shown by digoxin tests.

In interpreting the measurement results, all relevant clinical data must be taken into consideration.

Radioimmunoassays mark a considerable advance in the field of *in vitro* diagnostics. Their development has only begun, and further tests, especially for tumor-associated antigens, can be expected.

Radioimmunological examinations are coming into increasing use in clinics, laboratories, and also among individual practitioners. Various types of RIA, usually designated as "kits", are commercially available for determining hormones, plasma proteins, enzymes, vitamins, special antigens, and pharmaceuticals.

Some of these kits are relatively easy to use, and provide the desired results within a fairly short time, whereas others are more complicated, and require very precise use, with strict observance of reaction times and temperatures, ion intensity, and pH. RIA's are tests which make it possible to measure extremely minute quantities of a substance *in vitro*. This new method in clinical chemistry is far more sensitive than biological procedures.

High Sensitivity

Radioimmunoassays are among the most sensitive, specific, and accurate analytical procedures now available. One trillionth of a gram, or picogram (10^{-12} g) of a hormone can be demonstrated. Some substances can even be demonstrated down to a quantity of one quintillionth of a gram (10^{-18} g).

RIA's are superior to conventional biological tests, firstly because they are more sensitive, secondly because they are relatively quick and can be automated. Furthermore, with this method several samples can be examined within a comparatively short time. In regard to precision, RIA's are closer to chemoanalytic procedures than to biological tests.

Antigen-Antibody Reaction

RIA's combine the principles of radioisotope dilution analysis with those of the immunological antigen-antibody reaction; this means high sensitivity with high specificity. The method is based on the following phenomenon: Unlabelled antigen and radioactively labelled antigen, which do not differ from each other immunologically, compete with each other for binding sites on a certain specific antibody. This reaction is reversible, and obeys one of the classic laws of chemistry: the law of mass action.

After the solutions are mixed, a state of equilibrium, characteristic for the particular reaction partners, is established between the free antigen and free antibody on the one hand, and the antigen-antibody complex on the other hand. In other words, there is a state of equilibrium between bound and nonbound antigens and antibodies (Figs. 1 and 2).

RIA's use a limited amount of antibody; therefore, in addition to the complex, there is always free antigen present. If a certain quantity of a radioactively labelled antigen, i.e. a tracer, is used in such a reaction, the more unlabelled antigen is present, the less tracer will be bound, because of competition for the limited amount of antibody present. In RIA's, the labelled antigen and the antibody are kept constant.

The radioactivity of the hormone-antibody complex is reduced by adding unlabelled hormone. Simultaneously, labelled antigen is released and serves as a parameter for the amount of unlabelled antigen which is being sought, e.g. the amount of hormone present in the patient's serum.

Calibration Curve

Calibration curves are produced by means of standardized antigen, e.g. the hormone being examined. With these curves, the concentration of the antigen contained in the sample can then be determined (Fig. 3) (33).

Separation of the Antigen-Antibody Complex

For determination of concentration, the antigen-antibody complex must be separated from the nonunited reaction partners (free antigen and antibody). This separation can be carried out with various methods, such as centrifugation, precipitation, ion exchange, gel filtration, electrophoresis, adsorption, or agglutination.

Double Antibody Method

There are also test systems based on the so-called double antibody method. Here, a second antibody is used to precipitate the hormone-antibody complex. After preincubation with the first antibody, the second antibody is added. It reacts with the original antigen-antibody complex to form a larger precipitate complex: an antibody-antigen-antibody complex. This larger product, which is often designated as a "sandwich", is easier to separate, especially by means of centrifugation.

Other test systems have been developed on the basis of the so-called solid phase method. Here there are two possibilities: Either the antibody is firmly bound chemically to a neutral molecule, usually a polymer (e.g. cellulose or agarose) without loss of its specificity, or the antibody is attached to the wall of the reaction container, the so-called coated tube method.

The high sensitivity of radioimmunoassays is due to the use of radioactive isotopes, and also to the high affinity of the antibodies. The specificity of the method is due to the particular "fit" between the antigen and the antibody, which can be thought of as a "lock-and-key" pattern.

Determination of Hormones and Pharmaceuticals

RIA was originally developed for analyzing peptide hormones. In 1959, Yalow and Berson (50) first succeeded in determining insulin. In the meantime this procedure has been extended to other groups of substances, such as enzymes, globulins, and steroids, thus contributing greatly to progress in physiology, and especially in endocrinology. At present it is being used more and more in clinical work, where, in addition to the determination of various hormones, there is particular interest in running checks on the serum concentrations of various pharmaceuticals, e.g. digoxin and digitoxin.

Radioimmunometric Assays

In contrast to clinical RIA's, a so-called radioimmunometric assay is being developed. Here, the antibodies are labelled instead of the antigens, and are added in excess to the test system. The method is based on a simple principle, but its technique is comparatively complicated. Because of the excess of antibody, there is complete binding of all antigen molecules, and thus no competition between labelled and unlabelled antigen for the binding sites of the antibody, as there is in radioimmunoassays. The labelled antibody which is not used up is fixed to an immunoadsorbent after the reaction, and thus separated from the antigen-antibody complex which has formed. Radioimmunometric assays are very sensitive, and provide extremely precise measurements, as has been shown with such substances as IgG and ferritin.

In conclusion, it can be said that radioimmunoassays permit quantitative determination of serum components, especially hormones, at very low concentration levels, i.e. in the nanogram and picogram range. Certain complete kits are already available on the market, and are relatively easy to use.

The present tendency is towards a wider use of the RIA's already available, e.g. for determining Australia antigen and insulin. The production of RIA's for lipoproteins, immunoglobulins, and other plasma components, as well as for cyclic adenosine monophosphate and a number of enzymes, means a further extension into the field of clinical chemistry (Table 1).

It remains to be hoped that one day it will be possible to use radioimmunoassays for determining the carcinoembryonic antigen and perhaps other tumor-associated antigens as a screening technique for early diagnosis of cancer.

Determination of Immunoglobulins in Dermatoses

Using the radioimmunosorbent assay (RISA) (11, 17, 49), we analyzed serum from 238 patients with various dermatological diseases; 130 of these were patients with neurodermatitis constitutionalis. We also determined IgE in the serum of 51 patients with psoriasis vulgaris, 12 with urticaria, 10 with contact dermatitis, and some other cases. In order to determine our own standard IgE level, we analyzed the serum of 100 normal subjects without dermatological diseases or helminthic infections.

Results

The serum of our normal subjects contained an average of 163 U/ml of IgE (1 U is equivalent to 1 ng), with a range (± 2 SD) of 0-500 U/ml (32). Our average value is comparable with the published references: 179 ng/ml in a group of normal subjects (11); 129 ng/ml with a range of 0-460 ng/ml in cases of tubercular diseases (48); and 248 ng/ml with a range of 61.4-1000 ng/ml in non-atopic diseases (17). The level of IgE was raised in the patients with neurodermatitis; the highest level was greater than 40,000 U/ml (Fig. 4). The serum of these patients contained a mean value of 4559.4 U/ml of IgE. Of the patients with neurodermatitis, 56.9% had an IgE level of 1000-10,000 U/ml. However, 22.4% of this group overlapped with the values from normal subjects (11).

The mean value from patients with non-atopic dermatitis was found to be within the range of the group of normal subjects (51 cases with psoriasis vulgaris, average value 346.5 U/ml; 12 cases with urticaria, average value 215.8 U/ml; 10 cases with contact dermatitis, average value 223 U/ml).

Fixing the limit between normal and raised IgE levels at 1000 ng/ml (17), we found pathological results in 68.4% of our patients with neurodermatitis, as well as in 11.8% of the psoriatics. None of the patients with contact dermatitis had a raised IgE level.

Discussion

Among the 4 groups examined (neurodermatitis, psoriasis, urticaria, contact dermatitis), only the neurodermatitis group had a raised mean IgE value (9 times higher than the mean value of normal subjects). Of these patients with neurodermatitis, 68.4% had an IgE level of more than 1000 U/ml, and 77.4% had a value above 500 U/ml. Similar results have been published previously in the literature (19, 48).

In some non-atopic diseases, e.g. psoriasis vulgaris, mycosis fungoides, and eczema, we also found slightly raised IgE levels, as described in patients with persistent urticaria following penicillin, recurrent infections, and arteriosclerotic ulcer (19).

Radioimmunoassay for Digoxin

In treating cardiac insufficiency with digitalis, so-called full effective doses or levels are used for orientation. In clinical use, a full effective dose is that amount of digitalis required to compensate cardiac and circulatory insufficiency. The concept of full effective levels, which has also come into clinical use, does not, however, refer to the volume amount of blood or plasma, e.g. to 1 or 100 ml, but rather to the patient's entire body. The cardiac glycosides have a narrow therapeutic range. Their pharmokinetics can vary among individuals, or can vary in the same individual during long-term treatment, because of such factors as renal function, disturbances in electrolyte balance, or metabolic disorders. Intoxication with digitalis glycosides among over-digitalized patients is estimated to be from 7% to 20% (1, 14). Therefore it is desirable to have a means for measuring the plasma concentration of these drugs, especially digoxin, which is now used in most cases.

In recent times, chemical and biochemical methods have been developed for determining the therapeutic digitalis concentration in the serum or plasma, and for listing it in ng/ml. Such quantitative methods give the clinician a better check on his therapy, and permit early recognition of accumulation dangers. These methods have the following individual advantages:

1. Correction of dosage,
2. Recognition of incipient intoxication,
3. Aid in the etiological differentiation of disturbances in rhythm.

Material and Tests

Serum from patients on digoxin was taken in the morning on an empty stomach, more than 8 hours after the last tablet of digoxin had been administered the evening before. It can be assumed that during this period the digoxin level attains equilibrium between blood and tissue. We examined serum from 120 patients who had become optimally adjusted to a maintenance dose of digoxin derivative (β acetyldigoxin, β methyldigoxin). Hemolytic and icteric sera, as well as sera from patients with renal insufficiency or on additional steroid-hormone or spironolactone therapy, were precluded, as were sera from patients whose albumin concentration deviated from the normal range, or from patients who had already undergone diagnosis with radionuclides. The sera were either examined immediately after reception, or were stored in deep freeze until they were examined.

The examinations were carried out with 5 different digoxin RIA's commercially available in the Federal Republic. Two of them were designed to analyze digoxin labelled with ^{3}H, and the other 3 were for digoxin labelled with ^{125}I. Each ^{3}H-RIA had as its counterpart a ^{125}I-RIA from the same manufacturer. The manufacturer's operating instructions were closely followed in each case. A duplicate of each serum sample was determined with each of the 5 RIA's, designated with the anonymous terms A_1, A_2, B_1, B_2, and C. Of these, A_1 and B_1 were ^{3}H-RIA's, while A_2, B_2, and C were ^{125}I-RIA's.

Results

The digoxin level in the blood is, firstly, dependent upon the size of the dose and, secondly, upon the time at which blood is withdrawn after administration of the last dose. Profile determinations show that the concentration in the serum decreases only slightly after 6 hours (Fig. 5). At this time, resorption is ended, and there is equilibrium between the concentrations in the serum and in tissue. For this reason, determinations of concentration for clinical use should be carried out only after an interval of 6 hours following the administration of the last tablet.

Determination of the serum concentration makes it possible to evaluate the bioavailability of digoxin preparations (2, 5, 16, 28, 29, 38, 44). Here, after the customary digoxin preparations have been resorbed, the serum concentrations are determined and compared with one another. If resorption is not impaired, and the digoxin doses are the same, the concentration level in the serum will be determined by the galenic properties of the preparation. This type of bioavailability test is indicated whenever a patient is to be taken off one digoxin preparation and put on another, or when a new digoxin specialty is introduced. Fig. 6 shows an example of the positive availability of a new digoxin preparation in a patient during the saturation and maintenance phase.

The 5 RIA's produced varying results in the determination of digoxin concentration in the patients' sera. The mean values of all determinations of the same 120 sera in the individual RIA's showed clear differences (Table 2) (36, 37).

The difference in the results is greatest between A_1, A_2, and B_1, where the mean values differ by a factor of more than 2, i.e. the digoxin content of the serum of one and the same patient was shown to be more than twice as high in the one RIA as in the other. Except for the determinations carried out with RIA B_1, our mean values fall in the same range given by other investigators: 0.8-1.7 ng/ml (1, 4, 6, 7, 12, 15, 18, 27, 30, 39, 46, 47, 51). With a given confidence interval of 95%, only the RIA's A_1 and A_2, as well as B_2 and C, are statistically equivalent to each other. The correlation coefficient and the regression lines likewise differ, corresponding to the differences in the determinations of concentration (Fig. 7) (35).

Discussion

The deviations by a factor of 2 which we found in determinations of digoxin concentration in the serum of one and the same patient are not unique: The relatively few comparative studies found in the literature contain reports of similar discrepancies in smaller numbers of samples (3, 13, 25). For instance, 6 ^{125}I-RIA's carried out on the same serum showed digoxin concentrations ranging from 0.1 to 1.5 ng/ml, or from 1.8 to 4.1 ng/ml (25). There are numerous sources of error with RIA's: mistakes in pipetting and counting, errors resulting from varying incubation times with the antiserum or with dextran-charcoal, variations in the quality of the antiserum, cross-reactions with steroid components in the serum, differences of affinity between antisera and digoxin labelled with ^{125}I in comparison with antisera and unlabelled digoxin, nonspecific binding of the sera to the tracer, disturbances caused by radioactivity from previous diagnoses with nuclear techniques, etc.

Conclusion

Because of the differences we found in the results of determining the concentration of digoxin in patients' sera using different RIA's, we consider the following points important:

1. In reporting serum digoxin concentrations in medical letters and publications, the RIA used must be specified.
2. Each laboratory which carries out digoxin determinations should, in collaboration with the clinic, work out and announce its own guide-line values for the RIA used in regard to the optimal therapeutic range and also to overdoses.

Ausria-II-125®

Abbott Laboratories recently brought out a modification of their RIA under the trade name Ausria-II-125®. The technical modification consists in the use of antibody-coated, roughly pea-sized polystyrene pellets which, comparable to miniature billiard balls, are placed in the wells on an incubation plate together with the serum. The plate is covered with an adhesive strip and then incubated for only 2 hours in a water-bath at 45° C. The second incubation, lasting 1 hour, also takes place at 45° C. The serological modification consists in the use of human antibodies labelled with ^{125}I instead of guinea-pig antibodies.

In our opinion, the modified Abbott RIA offers the following advantages:

1. It avoids the application of the serum at the wrong site, e.g. too high on the wall of the tube, as was possible with older RIA's.
2. It shortens the test to 3 hours by reducing the incubation time, thus making it possible to decide on the same day whether, for example, a blood transfusion should be administered.

Our Investigations

The tests we carried out convinced us of the high sensitivity and specificity of the Ausria-II-125. We examined sera from blood donors with the Abbott RIA, and also with migration electrophoresis; the results are listed in Table 3. Of the 2499 sera examined, 3 were shown to be HB_sAg-positive with electrophoresis. These samples were also shown to be positive with the RIA, as well as 6 other sera. This is equivalent to a demonstration rate of 0.12% with migration electrophoresis, and 0.36% with the Ausria-II-125; these results agree with those given in the literature (42, 43, 52). In subsequent examinations at intervals of 3 to 6 weeks, the above-mentioned 6 cases remained negative in the electrophoresis test, while 1 sample (case 6) was only weakly positive in the RIA, and remained so during the following observation period. The 9 samples which were positive in the RIA were from clinically healthy subjects aged 20 to 38, with normal transaminase values and no history of hepatitis.

To verify the HB_sAg specificity, we examined the 6 discrepant sera under an electron microscope. HB_sAg was demonstrable in all 6 samples, whereas the complement-fixation reaction was positive in only one-half of them. Thus, in our examinations, the Abbott RIA did not show a falsely positive result in a single case.

Significance of HB_sAg Demonstration

The association of serum hepatitis with HB_sAg permits differential diagnosis of the two forms of hepatitis. In cases of serum hepatitis, HB_sAg is already demonstrable in the serum during the incubation stage, an average of 1 to 4 weeks before clinical symptoms appear, and, as a rule, before there is an increase in transaminase (8, 21, 23, 24, 40, 45). Thus, serum hepatitis can be recognized before it manifests itself clinically. Prognostically, the disappearance of HB_sAg from the serum can be interpreted as a sign of recovery (22). However, if the HB_sAg persists longer than 3 months after the hepatitis has become clinically manifest, it is quite likely that the disease has shifted to a chronic course (22, 31, 41).

The appearance of HB_sAg indicates the simultaneous existence of the hepatitis virus. Thus, an HB_sAg carrier should be considered to be infectious even if he has no history of hepatitis, and even if there are no pathological chemical or histological findings (20). In the case of a blood donor, this means removing his name from the list, since it has been shown that a transfusion of HB_sAg-positive blood caused an apparent or nonapparent post-transfusion hepatitis (serum hepatitis) in 74% of the recipients (10).

Peptide Hormones:

luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, prolactin, growth hormone, adrenocorticotropic hormone, neurophysin, arginine vasopressin, oxytocin, β melanocyte-stimulating hormone, parathyroid hormone, calcitonin, insulin, glucagon, gastrin, enteroglucagon, secretin, placenta lactogen, choriongonadotropin, erythropoetin, angiotensin I and II, renin, bradykinin.

Plasma Proteins:

albumin, IgE, IgA, IgM, IgG, lipoproteins, thyroxine-binding globulin, transferrin.

Enzymes:

chymotrypsin, trypsin, pepsinogen, fructose-1,6-diphosphatase, C-1 esterase.

Tumor-Associated Antigens:

α fetoprotein, carcinoembryonic antigen.

Specific Microbiological Antigens:

Australia antigen, oncogenic RNA-virus protein, Schistosoma-mansoni antigen.

Miscellaneous:

human myelin protein.

Haptenes:

Steroids: estradiol, progesterone, testosterone, aldosterone, desoxycorticosterone.
Pharmaceuticals: digoxin, digitoxin, morphine.
Thyroid hormones: triiodothyronine, thyroxine.
Miscellaneous: folic acid, cyclic adenosine monophosphoric acid.

Table 1: Compilation of various substances which can be determined at present by means of radioimmunoassay or radioreceptor assay (after J. Landon (26)).

	RIA A_1	RIA A_2	RIA B_1	RIA B_2	RIA C
n	120				
$\bar{x}$	1.36	1.39	0.61	0.96	0.84
± s	0.78	0.76	0.54	0.51	0.50

Table 2: Mean values and simple standard deviation of the individual values in ng/ml of sera from 120 patients whose digoxin concentration was determined in double measurements with 5 different RIA's. The greatest difference in the mean values is between RIA's A_1, A_2, and B_1; the quotient is more than 2.

No.	Patient	RIA	ME	CFR	EM
1	E.H.	+	-	(1:†128)	+
	(control)		-		
	1:1	+			
	1:10	+			
	1:100	+			
	(control)		-		
	1:1	+			
	1:10	(+)			
	1:100	-			
2	H.J.	(+)	-	-	+
	(control)	(+)	-		
	(control)	+	-		
	(control)	(+)	-		
3	D.Z.	+	-	(1:†128)	+
	(control)	+	-		
4	A.G.	+	-	(1:†128)	+
	(control)	+	-		
5	P.T.	+	-	-	+
	(control)	+	-		
6	H.B.	-	-		
	(control)	(+)	-	-	+
	(control)	(+)	-		
	(control)	(+)	-		

Table 3: Six radioimmunologically HBsAg-positive blood donors in synopsis with the results of migration electrophoresis (ME), complement-fixation reaction (CFR), and electron microscopy (EM). All 6 cases which were definitely, or suspected to be, positive in the Ausria-II-125 RIA were also positive in the electron-microscope test.

$$Ag^{*} + Ak \rightleftharpoons Ag^{*}\text{-}Ak$$
$$(F) \quad (F) \qquad (B)$$
$$Ag + Ak \rightleftharpoons Ag\text{-}Ak$$
$$(F) \quad (F) \qquad (B)$$

Fig. 1: General scheme of the reaction principle of the radioimmunoassay, with simultaneous presence of radioactively labelled and unlabelled antigen (after Yalow and Berson (36)). Ak = antibody, Ag = unlabelled antigen, Ag* = radioactively labelled antigen, B = bound share (= antigen-antibody complex), F = free share of the reaction partners (= nonbound Ak, Ag, and Ag*).

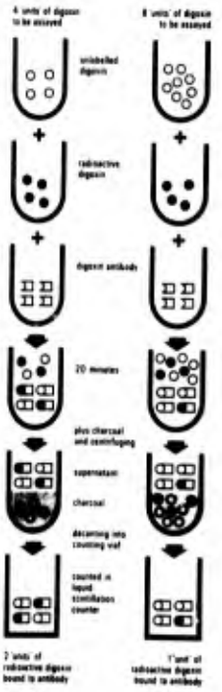

Fig. 2: Principle of the RIA, using a digoxin assay (Wellcome, England) as an example. The scheme shows the successive individual procedures and reaction stages. The vertical column on the right shows, in comparison with the one on the left, determination of the double amount of digoxin; here, at the end of the reaction, less radioactive digoxin is measured in the sample.

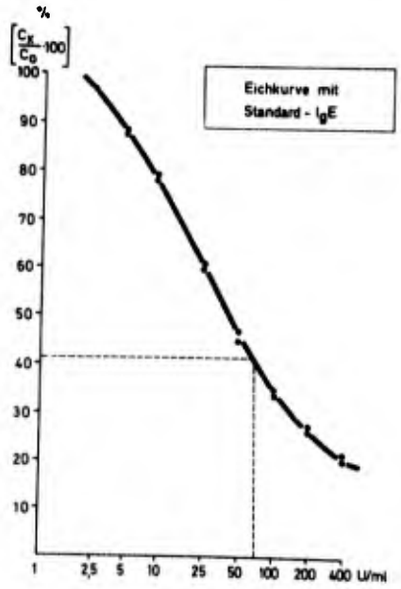

Fig. 3: Calibration curve on semilogarithmic scale for determining the IgE content of sera (Pharmacia, Sweden). The curve is produced on the basis of a dilution series with lyophilized standard IgE. The IgE concentration (U/ml) is plotted on the abscissa on a logarithmic scale. The IgE content is read off against a previously calculated percentage obtained from the ratio of the measured activity of each sample C_x to the blank value C_0. In the above example, the C_x/C_0 obtained by pulse measurement is 42%; on the curve, this is equivalent to 75 U of IgE per ml of serum.

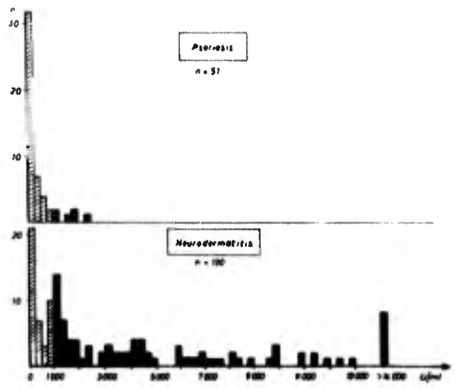

Fig. 4: Comparison of IgE concentration in neurodermatitis constitutionalis and psoriasis vulgaris. Concentrations of more than 1000 U/ml are indicated by the black columns.

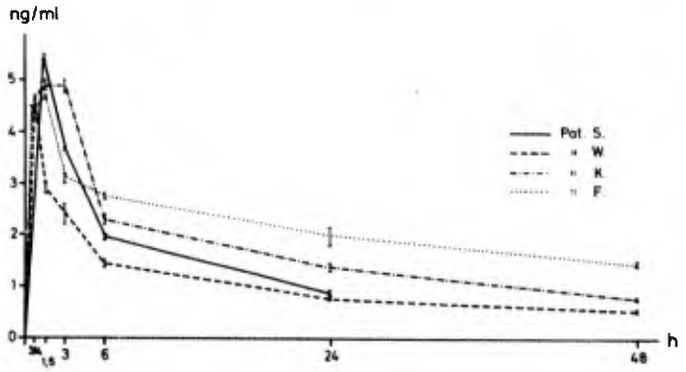

Fig. 5: Profile of digoxin concentration in sera of 4 patients over 48 hours after single oral dose of 1.5 g of pure digoxin (Boehringer, Germany) in crystalline form in a gelatine capsule, as determined with RIA C (^{125}I). Time change in concentration is less steep between 6 and 24 hours than between 3 and 6 hours; after 6 hours the digoxin is evenly distributed between blood and tissue.

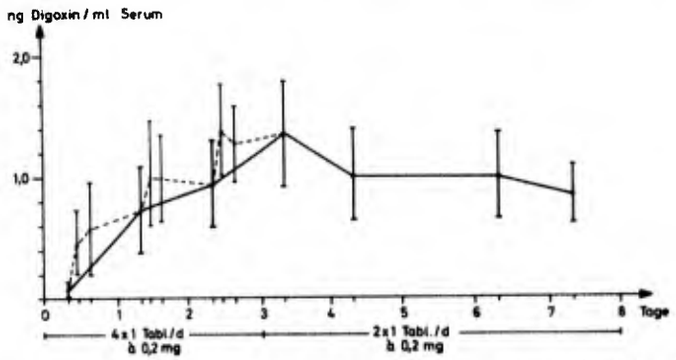

Fig. 6: Serum digoxin profile of an adult during oral saturation and maintenance dose of β acetyldigoxin. Steady increase in serum level proportional to the dose. (Measurement with ^{125}I-RIA B_2).

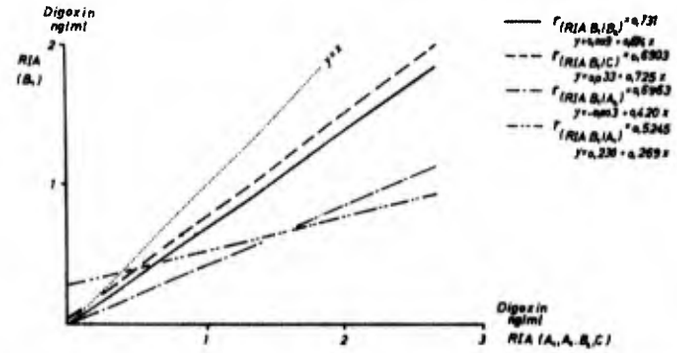

Fig. 7: Regression lines and correlation coefficients between digoxin determinations obtained with different RIA's. The individual RIA's are correlated with RIA B_1, in which the lowest digoxin concentrations were found (mean value: 0.700 ng/ml).

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THE ROLE AND LIMITATIONS OF RADIOIMMUNOASSAY AS A LABORATORY DIAGNOSTIC PROCEDURE

Robert L. Buchenauer, Major, USAF, BSC
Chief, Radioassay Laboratory Function
Epidemiology Division
USAF School of Aerospace Medicine
Brooks Air Force Base, Texas 78235

SUMMARY

The basic concepts of radioimmunoassay (RIA) and competitive protein binding (CPB) are reviewed. The characteristic features of sensitivity and specificity are discussed as they relate to the problems and limitations of test variability and biological interference in the performance of radioassays in the clinical laboratory. Potential problems due to improper patient preparation and specimen collection and handling are mentioned. A survey is presented of selected biological compounds that can currently be measured by radioimmunoassay and related techniques.

INTRODUCTION

In the evaluation of aircrew fitness, the aerospace medical physician relies on many of the established clinical laboratory procedures used in diagnosing disease. Radioimmunoassay (RIA) first developed for the measurement of hormones, has revolutionized the field of endocrinology. During the past several years this technology has expanded to include the laboratory quantitation of many other biological compounds in the fields of pharmacology, microbiology, hematology, oncology, and gastroenterology. RIA combines the specificity of an immunological reaction with the sensitivity of radiochemistry and increases the detection limits of a variety of biological substances into the nanogram (10^{-9} gm) and picogram (10^{-12} gm) range with previously unattainable precision.

Over the past decade RIA and related techniques have been useful in diagnosing various disease states. More than 200 substances are capable of being measured in the sub-nanogram range today, and this technology is progressing rapidly toward the time when RIA will be used widely in the presymptomatic recognition and prevention of diseases. Considerable information exists regarding RIA technology and its impact on clinical chemistry (1-5). The practicing physician must be fully acquainted with the operational parameters of RIA methodology in order to accurately evaluated laboratory results and correlate them with a clinical diagnosis.

HISTORY

The basic principles of competitive binding assays were first applied independently in the late 1950s by Berson and Yalow in the United States and by Ekins in England. The observation of Yalow and Berson (6) that low concentrations of insulin antibodies could be detected by their ability to bind radiolabeled insulin is the basis for all radioimmunoassay procedures in use today. Ekins (7), concerned with developing a general microanalytical technique applicable to a wide range of biological compounds, introduced a method for the assay of serum thyroxine utilizing a naturally occurring protein, thyroxine binding globulin (TBG), as a specific binding reagent. This particular technique is popularly called competitive protein binding (CPB). Ekins is credited for establishing much of the theoretical foundation upon which both RIA and CPB assays are based.

The use of different classes of specific binding substances by various researchers has given rise to a new set of terms in the literature (2). In addition to radioimmunoassay (RIA) and competitive protein binding (CPB), commonly used terms such as saturation analysis, displacement analysis, radioligand binding assay, radioassay, and radioreceptor assay all describe the immunochemical reaction in which a labeled and an unlabeled ligand compete for a site on a limited amount of antibody, receptor, or binder.

The two most common terminologies encountered in the clinical diagnostic laboratory are radioimmunoassay and competitive protein binding. Radioimmunoassay implies the utilization of an antibody as a binder substance while competitive protein binding is the terminology used to describe the utilization of a naturally occurring protein as the binder substance, (e.g. thyroxine binding globulin in the T4 assay and transcobalamine in the Vitamin B12 assay). Nevertheless, the theoretical principles and practical application of both these assays are similar and interchangeable.

BASIC CONCEPTS OF RIA

The concept of RIA is based upon an antigen-antibody reaction. Excess antigen (Ag) is allowed to react with a fixed quantity of antibody (Ab) thereby forming an antigen-antibody complex (Ag-Ab). This reaction is reversible and favors the formation of the antigen-antibody complex. Affinity constants (K_a) on the order of 10^{10} liters/mole are commonly obtained with good antibodies.

$$Ag + Ab \rightleftharpoons Ag\text{-}Ab$$

$$K_a = \frac{[Ag\text{-}Ab]}{[Ag]\,[Ab]} \cong 10^{10}$$

An identical radiolabeled antigen (Ag^*) is allowed to compete with the unlabeled antigen (Ag) for a common antibody (Ab). Since the ratio of the bound to the free radioactivity is equal to the ratio of the bound to the free unlabeled antigen, a quantitative basis exists to determine the amount of endogenous antigen present in an unknown biological material.

$$\begin{array}{lll} & \underline{\text{Bound}} & \underline{\text{Free}} \\ Ag + Ab \rightleftharpoons & Ag\text{-}Ab & + \quad Ag \\ Ag^* + Ab \rightleftharpoons & Ag^*\text{-}Ab & + \quad Ag^* \end{array}$$

$$Ag^*\text{-}Ab/Ag^* = Ag\text{-}Ab/Ag$$

In a typical radioimmunoassay, a given quantity of radiolabeled antigen is added to a series of tubes containing an unknown or standard amount of unlabeled antigen. The labeled and unlabeled antigen are incubated with a limited quantity of antibody for periods of thirty minutes up to several days, depending on the properties of the reagents of the specific assay system. During the incubation period the unlabeled antigen and the radiolabeled antigen compete for receptor sites on the antibody. In practice the antibody is usually diluted so that it will bind approximately 50% of the total radioactivity in the absence of endogenous antigen (see Fig. 1, Tube A). This tube is sometimes referred to as the initial binding, 100% binding, B_o, trace, or zero standard tube. As increasing amounts of endogenous or standard ligand are added the ratio of bound to free (B/F), bound to total (B/T), or bound to initial bound (B/B_o) decreases.

The isolation of the bound and free fractions is accomplished in several ways. One of the more popular separating techniques in RIA is known as the double antibody assay. In this method, a second antibody, capable of reacting with the primary antibody, is added to precipitate the bound fraction. A second method, particularly popular with steroids, is to adsorb the unbound fraction with dextran or hemoglobin coated charcoal. Talc or silica have also been used to adsorb the unbound fraction. Nonspecific precipitation of the bound fraction can be accomplished by the use of polyethylene glycol, ammonium sulfate, ethanol, etc. Some antibodies are rendered insoluble by coupling them to solid phase materials such as cellulose, Sephadex, polystyrene or glass beads. This latter technique shows great promise of simplicity, since the antibody can be coated to the inside of a test tube, thereby making the separation procedure a simple matter of decanting a tube. Lastly, some biological receptors are already bound to naturally occurring membranes, thereby facilitating easy separation by centrifugation.

The amount of radioactivity present in the bound fraction is inversely proportional to the concentration of the standard or endogenous antigen present. Tube A in Figure 1 contains no (zero) standard or endogenous antigen and therefore the antibody present will bind the maximum amount of radiolabeled antigen. Increasing the amount of standard or endogenous antigen decreases the amount of radioactivity observed in the bound fractions in tubes B and C. The bound or the free or sometimes both fractions are counted for a series of known standards and the data is plotted on a dose-response curve. The response variable B/F, B/T, or B/B_o is usually plotted against the dose or the logarithm of the dose.

CHARACTERISTICS OF RIA

One of the most prominent features of RIA is the extremely high sensitivity obtained in comparison to the more classical methods of analysis. RIA sensitivity is defined as the smallest amount of unlabeled antigen that may be distinguished from no (zero) antigen and, of course, is of the utmost importance when measuring very low concentrations of an antigen. As a rule sensitivities can be increased by using higher dilutions of an antibody; however, this usually results in a decrease in precision of the assay. Because of this extreme sensitivity, RIA can easily measure antigenic concentrations in the nanogram (10^{-9} gm) and picogram (10^{-12} gm) range. A second characteristic of RIA is specificity. This refers to the ability of the antibody to distinguish the substance of analytical interest from all other substances. It is emphasized that a particular antigen will induce the formation of multiple or heterogenous antibodies. Consequently a specific antigen can combine with multiple antibodies to various degrees which can lead to a source of error in estimating endogenous hormone concentrations. This same property, which led to the discovery of various forms of insulin (8), has also resulted in discrepancies in assaying for insulin by RIA. Two different antigens having similar structural features may cross-react with the antibody and give spurious results. For example, the glycopeptides, follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), luteinizing hormone (LH) and human chorionic gonadotropin (HCG) have similar structural characteristics and cross-react with an antibody directed against TSH (9). Even chemically unrelated drugs and hormones such as thyroxine and diazepam may also cross-react (10). Nonspecific factors in biological fluids modify the rate of the primary antigen-antibody reaction. These include such factors as ionic strength, pH, heparin, urea, excessive bilirubin concentration, high temperatures, and the composition of the incubating medium. The general quality of a radioimmunoassay is primarily determined by the quality of the antibody. Specificity is a function of the accuracy of the antibody in differentiating one substance from another, while sensitivity is determined by the avidity of binding between the antigen and antibody.

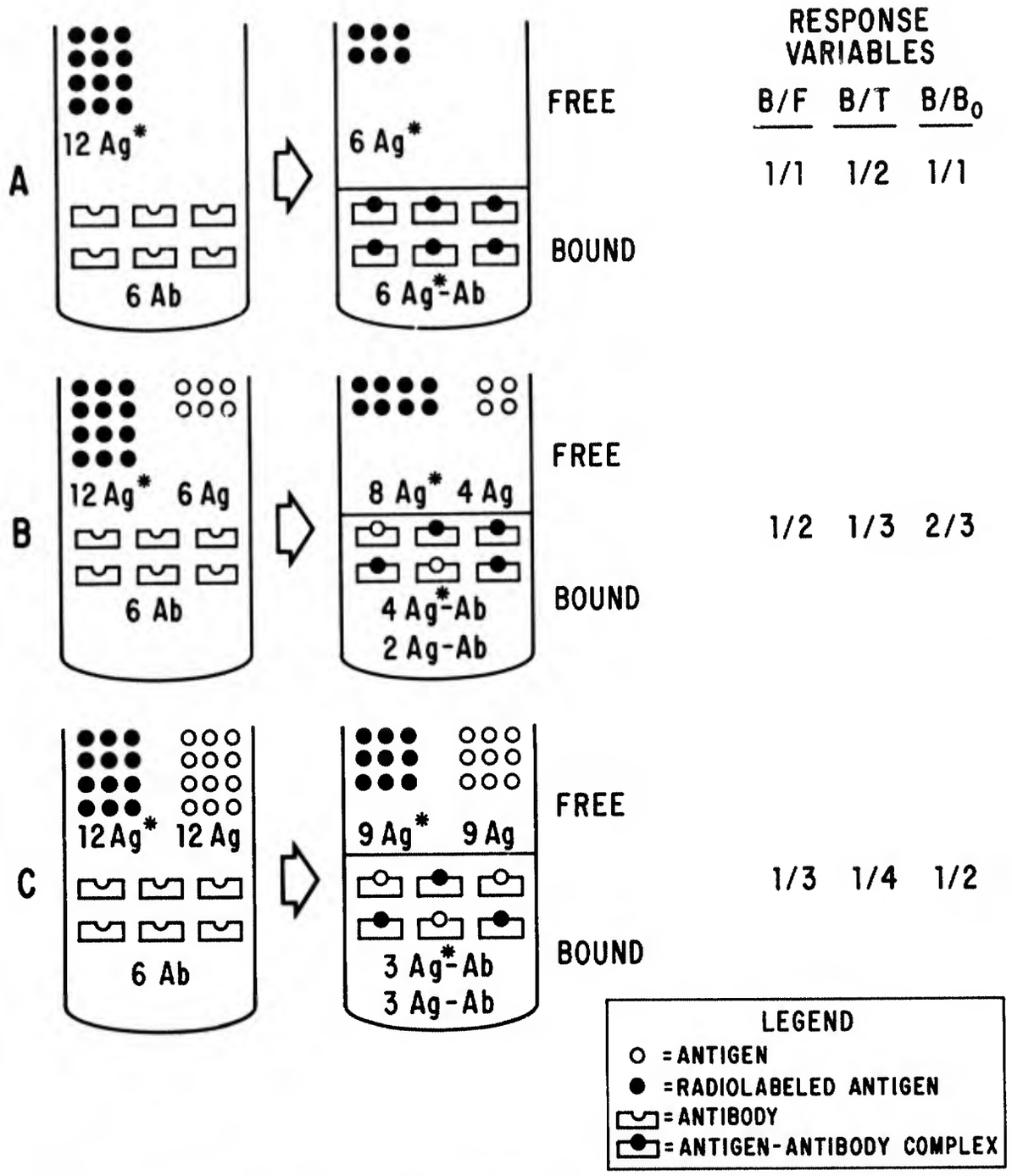

FIGURE 1. SCHEMATIC REPRESENTATION OF RADIOIMMUNOASSAY

POTENTIAL PROBLEMS IN RIA

In reaching a definitive diagnosis, the practicing physician must be constantly aware that radioimmunoassay measures an immunological and not necessarily a biological response. Various immunoreactive but biologically unreactive hormone fragments may react with an antibody in an immune system. For example, parathormone is metabolized into at least two biologically inactive fragments, an amino terminus and a carboxy terminus. This latter fragment competes for antigenetic determinates on an antibody directed against parathormone and consequently interferes with the assay for parathormone (11). Another potential source of interference in RIA is the measurement of less biologically reactive prohormones. In the RIA of insulin the structurally similar proinsulin molecule competes with the insulin molecule for antigenetic sites on the antibody and hence tends to falsely elevate insulin values. Additionally, the presence of autoantibodies to insulin in patient serum may result in falsely lowered insulin values in certain assay systems. The diagnostician must not only be aware of cross-reacting similar antigens in a given assay system but also the degree of cross-reactivity. Since cross-reactivity may vary with dilution, it is important that the dilution at which the cross-reactivity was measured be known. While most of these problems have been resolved or minimized, it is important to realize that similar problems may be reported in the future in other assay systems. These potential problems should be an incentive to encourage the physician to work closely with laboratory personnel in reaching a definitive diagnosis based on results of RIA.

Adrenocorticotropin (ACTH)
Aldosterone
Amphetamines
Androsterone
Angiotensin I and II
Antihemophilic Factor: Factor VIII

Barbiturates
Bradykinin

Calcitonin
Carcinoembryonic Antigen (CEA)
Cholesterol
Corticosterone
Cortisol
Cortisone
Cyclic AMP, GMP, IMP, UMP

Dehydroepiandrosterone (DHEA)
Deoxycorticosterone (DOC)
Deoxyribonucleic Acid (DNA)
11-Desoxycortisol
Diethylstilbestrol
Digitoxin
Digoxin
Dihydrotestosterone (DHT)
Diphenylhydantoin
Dopamine
Dopamine β-Hydroxylase

Erythropoietin
C_1 Esterase
Estradiol
Estriol
Estrone

Ferritin
α-Fetoprotein
Fibrinogen
Folic Acid (Folate)
Follicle Stimulating Hormone (FSH)
Fructose 1, 6 diphosphatase

Gastric Inhibitory Peptide (GIP)
Gastrin
Gentamicin
Glucagon
Gonadotropins

Hageman Factor
Hepatitis B Antibody
Hepatitis B Antigen
Hepatitis Associated Antigen (HAA)
Histocompatibility Antigens (HL-A)
Human Chorionic Gonadotropin (HCG)
Human Chorionic Somatomammotropin (HCS)
Human Growth Hormone (HGH)
2-Hydroxyestrone

Anti-D-Immunoglobulin
Immunoglobulins (IgE), (IgM), (IgG)
Insulin
Intrinsic Factor
Iron

Lipotropins
Long-Acting Thyroid Stimulator (LATS)
Luteinizing Hormone (LH)
Luteinizing Hormone Releasing Factor (LRF)
Lysergic Acid Diethylamide (LSD)

Marijuana
Medroxyproesterone Acetate
Melanocyte Stimulating Hormone
Methadone
Methaqualone
Morphine
Morphine/Barbiturate
Motilin

Norepinephrine
Neurophysin

Oabain
Oxytocin

Pancreozymincholecystokinin
Parathormone (PTH)
Penicillin
C-Peptide
Placental Alkaline Phosphatase
Plasminogen and Plasmin
Plasma Renin Activity
Progesterone
Prolactin
Prostaglandins
Prothrombin

Rabies
Retinol-Binding Protein
Rheumatoid Factor
Messenger Ribonucleic Acid

Secretin
Serotonin
Staphylococcal Enterotoxin A

Testosterone
Thyroxine (T4)
Thyroxine Binding Globulin
Thyrotropin (TSH)
Transcobalamin
Transferrin
Triiodothyronine (T3)
D-tubocuranine
T3 Uptake

Unsaturated Iron Binding Capacity (UIBC)
Urinary Albumin

Vasoactive Intestinal Peptide
Vasopressin
Viral Agents-Type C
Vitamin B12
Vitamin D3

TABLE 1. SUBSTANCES MEASURABLE BY RIA AND RELATED TECHNIQUES (12, 13)

Unfortunately, we often find that the clinical laboratory has taken every precaution to develop a highly specific, very sensitive and precise assay to obtain an accurate result, but the results obtained are invalid due to improper preparation of the patient or improper collection and handling of the specimen. Many factors influence various circulating hormone concentrations. Position and venous occlusion influence plasma IgE concentrations; insulin, glucagon, and gastrin are markedly influenced by food; many hormones, including ACTH, have a marked circadian rhythm; posture and salt intake affect plasma renin activity. Some hormones are influenced by physical activity while others are secreted in response to stress. In the absence of specific information to the contrary, biological samples should normally be drawn from a rested, fasted subject at a set time during the day. One should also be aware of possible radioactive contamination of plasma samples by previously administered radioactive diagnostic reagents. The presence of other radioisotopes in the plasma will seriously affect the accurate quantitation of radioactivity in a typical RIA procedure. Much of the information in relation to antigen stability required for correct handling of samples is either incomplete or unavailable. Some hormones such as ACTH are rapidly destroyed in whole blood. In the Angiotensin I assay, plasma must be drawn in a chilled vacutainer containing an enzyme inhibitor, immediately spun down and frozen at -20°C in order to prevent enzyme and substrate degradation. Visible hemolysis may lead to a marked reduction in measuring insulin concentrations. Plasma, as compared to serum, offers the advantages of rapid separation and hence less chance of hemolysis. However, knowledge of anticoagulant interference in the particular RIA is essential. In the absence of specific knowledge to the contrary, plasma or serum samples should be separated as soon as possible and immediately frozen and stored at -20° in a non self-defrosting freezer. Multiple freeze-thaw cycles should be avoided on all samples as well as antibodies and antigens, especially since the act of freezing and then thawing may activate proteolytic enzymes.

Most research institutions and university hospitals have the facilities and the staff to develop their own RIA methodologies. However, most hospital clinical laboratories do not have the trained personnel and expertise in RIA and consequently must rely on commercial kits and components. The recent proliferation of these commercial kits as well as the availability of relatively low cost laboratory instrumentation have made RIA an attractive package for the small hospital clinical laboratory. In the haste to compete for this potentially explosive market, commercial kits have been released on the market which suffer from the lack of quality control from the manufacturer as well as the lack of adequate research in establishing normal values. Since the source of each manufacturer's antibody reagents, standards, and reference control is usually different, it is of little wonder that results from one manufacturer's kit and the next do not agree well. These differences will not be resolved until a uniform national policy in reagent and antibody preparation is adopted. In the United States, the Food and Drug Administration is attempting to regulate the quality of new RIA kits being developed.

In a time of spiraling medical costs, it is remarkable that the major improvement of RIA has resulted in significant cost savings. The improved quality and precision of an RIA result combined with automatic pipetting, counting, and calculating equipment have helped to keep costs of RIA procedures to a minimum. The key in keeping costs low in RIA is volume and automation. Unfortunately, the volume of samples required for an economical assay is one of the most frequently overlooked parameters when deciding to perform an RIA in a clinical laboratory, and the procedures cost more than expected or the assays are run less frequently than originally anticipated.

APPLICATION OF RIA

Radioimmunoassays have been applied to an extremely broad range of biological measurements. At present there are over 200 substances which are now measurable by radioassay, and it has been estimated that in the next decade as many as 30-50% of laboratory requests will be available by RIA. Some of the substances which are measurable by RIA and related techniques are listed in Table 1. A comprehensive directory of available commercial radioassay test kits and components including approximate price information was published in September 1974 (12).

CONCLUSION

Radioimmunoassay and related techniques, with their inherent sensitivity, specificity, precision, and wide applicability, have played and will continue to play an important role not only in the diagnosis and treatment of disease but also in the presymptomatic recognition and prevention of disease. With further refinements in antibody production and RIA methodology, highly sensitive and specific assays will eventually be made available which will eliminate much of the extraction and cross-reaction problems now being experienced. However, the aerospace medical physician must be thoroughly indoctrinated in the theory and be familiar with the interpretation of radioimmunoassay results in order to facilitate a correct diagnosis of disease states.

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POSSIBILITE DE L'UTILISATION DES MOYENS DE SIMULATION DES AGRESSIONS AERONAUTIQUES POUR L'EXPERTISE MEDICALE DU PERSONNEL NAVIGANT.

par

le Médecin en Chef J. DEMANGE
le Médecin en Chef R. AUFFRET
le Médecin Principal B. VETTES
le Médecin J.L. POIRIER

LABORATOIRE DE MEDECINE AEROSPATIALE - CENTRE D'ESSAIS EN VOL - 91220 BRETIGNY/ORGE

RESUME

L'aptitude médicale d'un pilote peut être difficile à préciser dans certaines circonstances :

- Entrée en école (Anthropométrie.....).
- En cours d'études (Malaises en vol....).
- Après une blessure (Diminution de la force physique....).
- Après une maladie (Troubles physiologiques ou psychophysiologiques...).
- Avec l'âge etc....

Les examens médicaux cliniques, radiologiques et biologiques permettent le plus souvent de décider de l'aptitude du pilote, mais quelquefois en France, le Centre d'Expertise du Personnel Navigant fait appel au Laboratoire de Médecine Aérospatiale. Ce Laboratoire par ses mesures physiologiques et ergonomiques faites sous agressions simulées (Accélérations, vibrations, etc....) peut permettre de décider de l'aptitude médicale en cas de doute.

I. - INTRODUCTION

L'appréciation de l'aptitude médicale d'un pilote ou d'un autre membre du personnel navigant peut être délicate à définir sans ambiguïté à certaines occasions de sa vie professionnelle.

- A l'admission en école,
- Au cours de l'instruction en école :

  (malaises ou troubles en vol, surtout sous l'influence des accélérations....),
- Après une blessure : (diminution de la force physique ou de l'efficacité des mouvements).
- Après une maladie ou un accident aérien (troubles physiologiques ou psychophysiologiques divers, survenant surtout en vol à la reprise de l'activité).
- Sous l'influence présumée de l'âge, etc....

Les examens médicaux cliniques, radiologiques et biologiques permettent le plus souvent de se prononcer sans trop d'hésitation dans un sens ou dans l'autre, mais dans un certain nombre de cas, les médecins des hôpitaux et des centres d'expertises hésitent ou prononcent une décision d'aptitude limitée (Limitation dans le temps du nombre et de la difficulté des vols ; interdiction de vol en monoplace, etc...) sans toujours penser à utiliser les possibilités de simulation de vol et d'explorations fonctionnelles que permettent les installations d'un Laboratoire spécialisé comme celui du Centre d'Essais en Vol. Selon le cas, ce laboratoire pourra effectuer différents examens:

- Etude ergonomique des gestes nécessaires au pilotage.
- Mesure de la force musculaire exercée, soit sur les pédales et palonniers, soit sur les poignées de déclenchement du siège éjectable (au sol et en centrifugeuse sous accélérations + Gz).
- Etude des réactions physiologiques sur plateau vibrant et en centrifugeuse.
- Etude de la "performance humaine" par tracking, ou mieux pilotage simulé.

2. - ETUDE DES GESTES DE PILOTAGE ET DE LA FORCE MUSCULAIRE.

Au cours de la visite médicale d'admission en école de pilotage, l'application stricte et mathématique des normes statistiques anthropométriques exigées entraînerait l'inaptitude définitive d'un certain nombre de candidats. C'est pour cette raison que le Centre d'Expertise Principal du Personnel Navigant demande régulièrement au LAMAS d'effectuer une expertise permettant parfois de nuancer la décision, un exemple en est fourni par l'appréciation de la longueur de bras nécessaire au pilotage d'avion de combat et à la mise en oeuvre des moyens de sécurité : accessibilité et préhension des poignées commandant l'éjection.

L'étude consiste à placer le candidat une fois entièrement équipé : combinaison de vol, casque et gants,sur un siège éjectable placé dans une cabine d'avion accrochée au bras de la centrifugeuse.

Une fois sanglé sur son siège il est demandé au sujet d'effectuer toutes les manoeuvres nécessaires au pilotage : maniement du manche dans toutes les directions, action sur tous les boutons du tableau de bord et sur les poignées du siège éjectable. Toutes ces manoeuvres sont réalisées dans toutes les positions possibles du siège (position extrême basse, intermédiaire et extrême haute). Un résultat satisfaisant (y compris sous accélération + Gz) peut permettre l'admission en école d'un certain nombre de sujets qui présentaient des normes anthropométriques limites.

Après un accident ayant entraîné des fractures, un pilote peut présenter une diminution des mouvements ou de la force musculaire de ses membres.

La force musculaire du membre inférieur d'un tel sujet peut être mesurée par l'étude de la pression exercée par ce membre sur un système dynamométrique monté sur des palonniers d'aéronefs.

La décision d'aptitude est alors prise par le Médecin, soit immédiatement, soit après un nouveau contrôle quelques mois après des vols en double commande.

De même, le LAMAS a mis au point un dispositif permettant de mesurer l'effort développé par un pilote lors de l'action sur les commandes haute et basse du siège éjectable Martin Baker. (Réf. 1).

Un dispositif spécial simulant entièrement le déclenchement de l'éjection a été conçu : il comprend une cinématique avec ressort permettant de tarer l'effort demandé et reproduisant en une seule action les 2 mécanismes de départ de la verrière et du siège (fig. 2).

La mesure des efforts est effectuée par des systèmes dynamométriques respectant le déplacement des poignées, ils comprennent :

- un dynamomètre à jauge de contrainte inserré dans la commande haute (fig.3).
- un capteur de déplacement pour mesurer en correspondance le déplacement utile de la pince,
- une poignée basse dynamométrique dont l'aspect extérieur est identique en tous points à la poignée basse rigide du siège éjectable Martin Baker et qui renferme un dispositif à jauges de contraintes.

Les essais physiologiques ont été réalisés dans la nacelle de la centrifugeuse équipée du siège muni de son dispositif spécial et de ses dynamomètres (fig. 1). Ils ont porté dans un premier temps sur la poignée haute (fig. 4) et dans un deuxième temps sur la poignée basse. Chaque essai comprend 2 séries : l'une à 1 Gz, l'autre à + 3 Gz en centrifugeuse. Au cours du lancement le contrôle est assuré par télévision avec enregistrement sur magnétoscope (ce qui permet d'observer les attitudes et positions du pilote sous accélérations) et par enregistrement de la valeur de la force exercée sur les poignées.

Des études antérieures ont précisé la valeur de la force minima nécessaire au déclenchement des poignées (Environ 25 daN pour la poignée haute, et 40 daN pour la poignée basse) et surtout ont montré qu'un minimum d'entraînement des pilotes était nécessaire pour l'accomplissement d'un geste efficace (Effort prolongé à fond pour la poignée haute ; effort brusque pour la poignée basse). En éliminant donc le facteur dû à l'apprentissage, l'essai décrit permet d'apprécier la possibilité physiologique d'un sujet pour effectuer le déclenchement de ces gestes de survie (même sous accélération) avec une cinétique et une force suffisante ; le maintien de l'aptitude médicale du pilote peut en dépendre.

3. - MESURES PHYSIOLOGIQUES OBJECTIVES SOUS ACCELERATION

Il arrive qu'un élève pilote supporte mal les évolutions serrées de son avion ou qu'un pilote confirmé déclare avoir constaté une diminution nette de sa tolérance aux accélérations (+ Gz surtout). Les examens médicaux généraux ou spécialisés (O.R.L.)ne mettent pas souvent en évidence des causes bien nettes et il semble logique d'envisager une exploration fonctionnelle en centrifugeuse. Une étude progressive de la tolérance aux accélérations pourra être entreprise ; le sujet sera centrifugé à différents niveaux d'accélération, avec ou sans vêtement anti G, et avec un lancement plus ou moins brutal grâce à la catapulte à air comprimé du Laboratoire de Médecine Aérospatiale qui permet d'appliquer un Jolt pouvant atteindre 15 G/sec. Classiquement l'altération de la vision périphérique, doit permettre d'apprécier la tolérance aux accélérations + Gz mais cet examen repose sur la participation du sujet qui peut essayer d'améliorer ses réponses en utilisant sa vision centrale (l'élève pilote dans un souci compréhensible d'être reconnu apte) ou qui peut au contraire dégrader plus ou moins inconsciemment ses réponses ("Vieux pilote" en butte à des problèmes psychologiques ou à une baisse de motivation). Il est pourtant important de mettre en évidence ou non une altération physiologique circulatoire afin de pouvoir prendre une décision thérapeutique médicale ou psychologique et une décision administrative (réorientation, inaptitude temporaire, déclassement, etc..)

Dans ce but le Laboratoire a préconisé d'utiliser des mesures objectives permettant de suivre les variations des principaux paramètres circulatoires : (Réf. 2).

a) - Mesure de la pression artérielle par enregistrements des bruits de KOROTKOFF.

b) - Mesure de la fréquence cardiaque et des variations du volume d'éjection systolique par plethysmographie électrique thoracique. Cette méthode de mesure d'impédance électrique qui ne nécessite que la pose d'électrodes métalliques sur le thorax devant l'aorte et qui est présentée en détail dans une autre communication à ce même PANEL (COLIN - LANGLOIS - DEMANGE) permet très probablement de suivre l'évolution du débit cardiaque chez des sujets sans affections cardiovasculaires importantes. La précision de la mesure semble suffisante pour apprécier les variations de volume d'éjection systolique comme le montre les figures (5-6-7) ou l'on suit l'effet d'une accélération de + 3 Gz ; le volume d'éjection systolique apprécié par la dilatation aortique diminue d'environ 50 % du fait de l'accumulation de sang dans les membres inférieurs et de la réduction du retour veineux vers le coeur ; L'accélération de la fréquence cardiaque compense en grande partie pour maintenir un débit cardiaque convenable ; le gonflage du vêtement anti-G ramène presque instantanément la valeur d'origine du volume d'éjection systolique. (Réf. 3).

c) - Mesure des "pulsations" artérielles cérébrales par rhéographie (donc aussi mesure d'impédance électrique),qui dans l'état actuel de nos connaissances,ne peut nous permettre qu'une évaluation approximative de l'efficacité de la circulation cérébrale ; comme le montre les figures 8-9-10, la disparition des battements artériels est sensiblement contemporaine de l'apparition du "voile gris" signalé par les sujets.

Ces méthodes de mesure ne sont pas toujours faciles à mettre en oeuvre en centrifugeuse si l'on ne dispose pas d'excellents contacts tournants et d'appareils de mesure résistants aux accélérations, placés à proximité des sujets et règlables à distance du poste de contrôle.

Ces mesures effectuées en centrifugeuse ont permis,par exemple, de préciser l'origine de l'apparition des troubles ressentis en vol par un élève pilote ; ce dernier, en centrifugeuse, a signalé un voile gris à 3 Gz et simultanément on a enregistré un tracé rhéoencéphalographique identique à celui de la figure 10 et une pression artérielle beaucoup plus basse que la majorité des sujets centrifugés à 3 G (10/6). La distance coeur-cerveau de ce sujet longiligne, était en effet supérieure à 45 cm, ce qui est une des causes probables de sa désadaptation cardio-vasculaire. Au contraire, un tracé rhéoencéphalographique à 5 Gz comme celui de la figure 9 permet d'éliminer une mauvaise adaptation circulatoire d'un pilote et doit faire suspecter une autre origine de la baisse de tolérance aux accélérations.

4. - MESURES OBJECTIVES SOUS VIBRATIONS

Le vol à grande vitesse et basse altitude des avions de combat entraîne l'apparition de vibrations de très basses fréquences (1 à 3 Hz). La baisse de tolérance d'un pilote (fatigue,diminution de la capacité de travail, etc....) nécessitera bien sûr un examen médical et biologique approfondi, mais il est logique de vouloir tester ce pilote au moment même où il subit les vibrations. Comme pour les accélérations, une telle étude ne peut se faire qu'en laboratoire et actuellement nous mettons au point les moyens nécessaires :

- Générateur de vibration T.B.F.(Vérin) actionné soit par programme régulier (sinusoïde)soit par une bande magnétique reproduisant les accélérations périodiques enregistrées à bord d'un avion effectuant les vols à grande vitesse et basse altitude.

- Mêmes mesures physiologiques que celles effectuées en centrifugeuse.

- Mesures de l'altération de la performance humaine par l'utilisation d'un test de poursuite compensée (TRACKING sur ILS) associé à la mesure de temps de réaction simples (reconnaissance de feux colorés en vision périphérique). (Réf.4).

La mise au point du moyen de simulation des vibrations et des protocoles de mesures physiologiques n'est pas encore terminée mais déjà on peut prédire son intérêt : certains sujets présentent des altérations circulatoires sous vibrations T.B.F. (Baisse de Pression artérielle et de débit cardiaque) qui évidemment seront plus importantes en cas de déficiences physiques transitoires ou permanentes. D'autres sujets diminuent surtout leur performance (temps de réaction) lorsqu'ils sont fatigués ou sous l'influence d'agressions surajoutées:(alcool, préoccupations professionnelles ou familiales, etc...).

5. - CONCLUSION

Un Laboratoire de Médecine Aérospatiale bien équipé en moyens de simulations : (Centrifugeuse, générateur de vibration, etc...) et en moyens de mesures (Examens physiologiques et psychophysiologiques) peut apporter une contribution capitale aux expertises médicales difficiles du personnel navigant ; il semble logique dans les cas douteux de ne prendre une décision médicale et règlementaire qu'après avoir "testé"le pilote dans des conditions de simulation reproduisant au mieux les agressions rencontrées dans sa vie professionnelle. De plus, ce laboratoire offre la possibilité de répéter ces examens et donc de suivre d'une manière objective les évolutions transitoires favorables ou défavorables et les effets éventuels du vieillissement.

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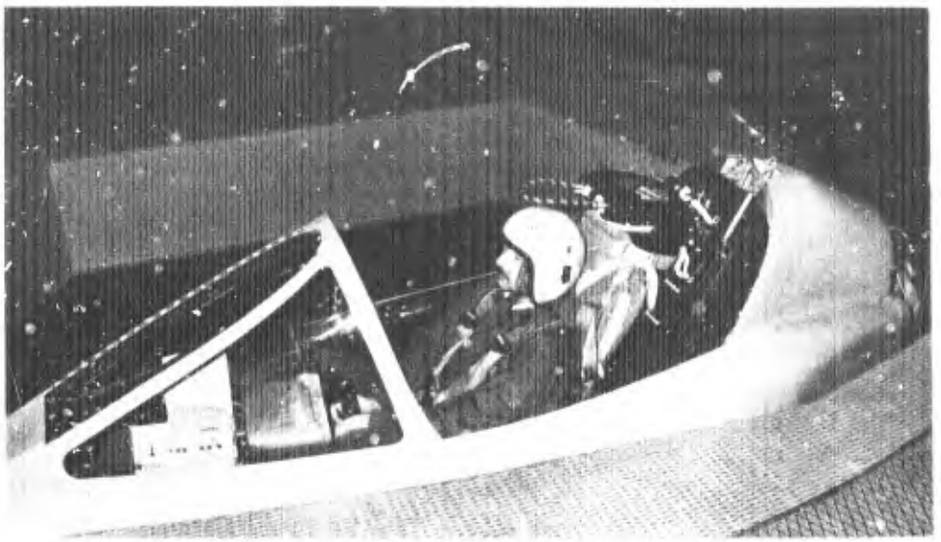


FIG. 1 : Nacelle de type avion accrochée au bout du bras de la centrifugeuse (on remarque le dynamomètre placé à la partie supérieure du siège).

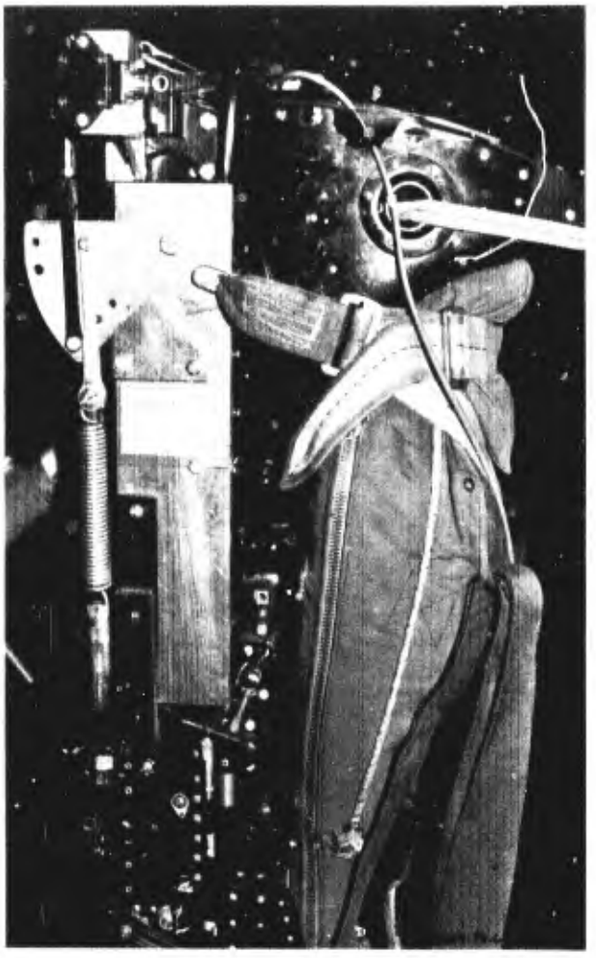


FIG. 2 : Cinématique avec ressort.

INSTALLATION D'ESSAI

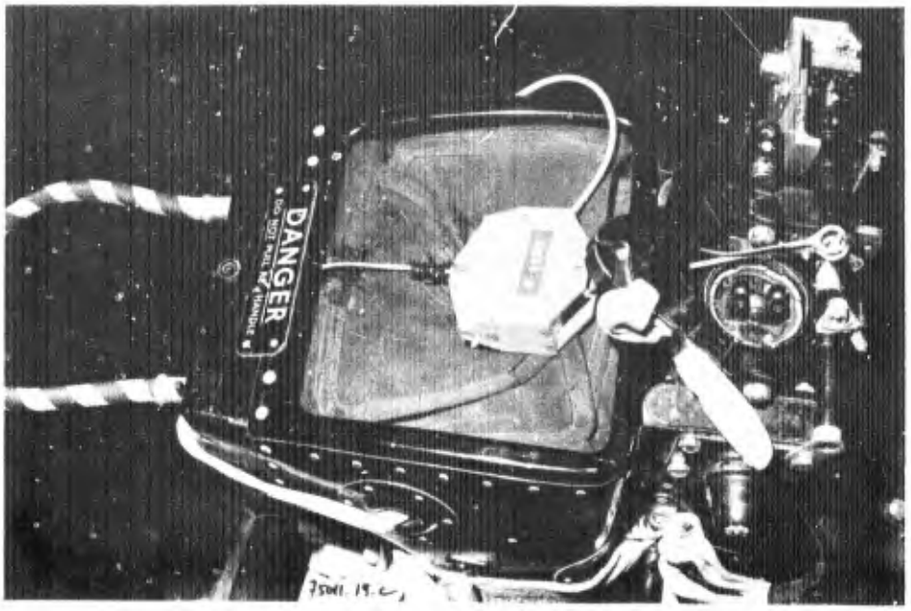


FIG. 3

Capteur de déplacement.

Pince articulée avec les 2 câbles de commande.

Dynamomètre inserré dans la commande haute.

FIG. 4 a

Action sur la poignée haute.

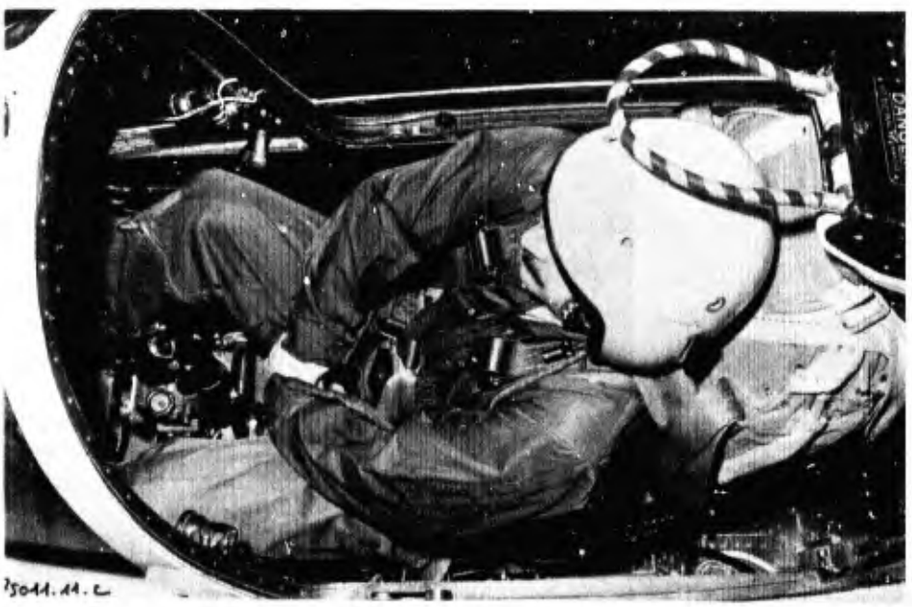


FIG. 4 b

Action sur la poignée basse.

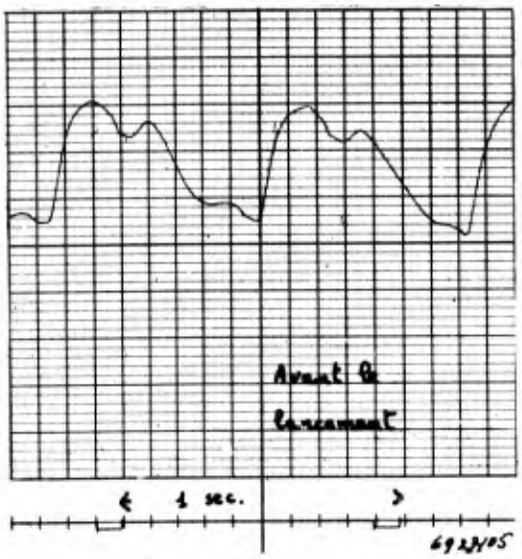


FIG. 5 : (+ 1 Gz).

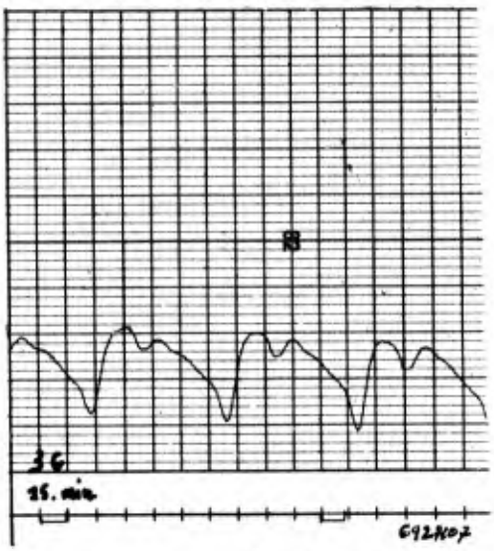


FIG. 6 : (+3 Gz Vêtement anti-G non gonflé).

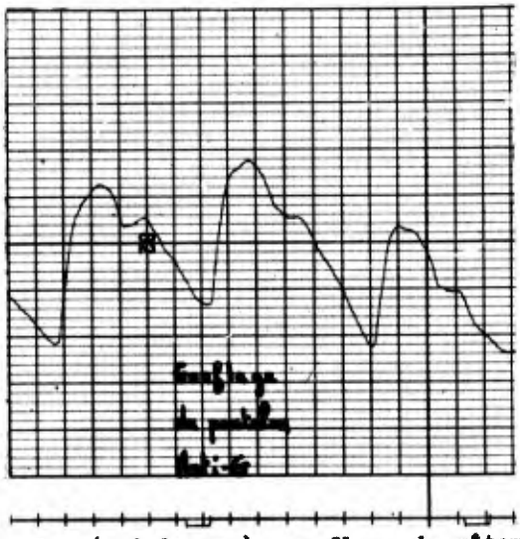


FIG. 7 : (+ 3 Gz après gonflage du vêtement anti-G)

PLETHYSMOGRAPHIE ELECTRIQUE DE L'AORTE.

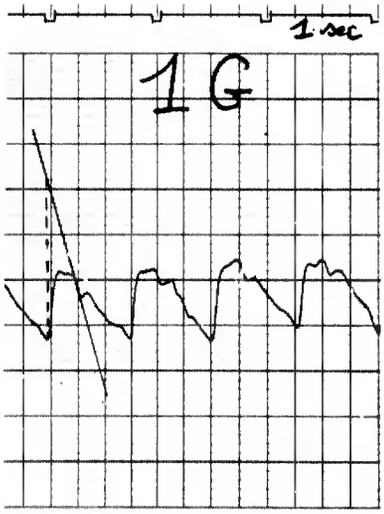


FIG. 8 :(+ 1 Gz)

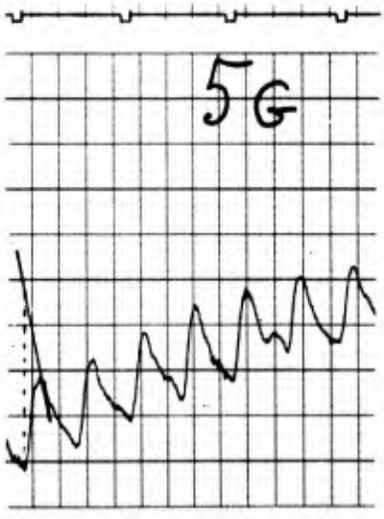


FIG. 9 : (+ 5 Gz)

FIG. 10 : (+ 5 Gz voile gris)

RHEOENCEPHALOGRAPHIE.

AVIATOR PERFORMANCE: BIOCHEMICAL, PHYSIOLOGICAL, AND PSYCHOLOGICAL ASSESSMENT OF PILOTS DURING EXTENDED HELICOPTER FLIGHT

Kent A. Kimball, Ph.D. and David B. Anderson, Ph.D.

U. S. Army Aeromedical Research Laboratory
Fort Rucker, Alabama 36362

SUMMARY

This investigation was conducted to provide information on the physiological, psychological and performance effects of extended helicopter flight. Measurements of biochemical, physiological and psychological parameters were obtained and compared with inflight performance measures obtained by the USAARL Helicopter Inflight Monitoring System. Six rotary wing aviators performed extended daily flight missions for a period of five days. In addition, when not flying, various psychological tests were administered. Physiological and biochemical monitoring were conducted throughout the five day period. Ss were on a controlled diet and slept approximately three hours each night. This paper presents preliminary findings with regard to performance, biochemical, physiological and psychological parameters.

INTRODUCTION

The tactical situation can often require long hours for both Army rotary wing crews and aircraft. However, little is known about the physiological, psychological and performance effects of extended helicopter flight. Currently, the Army has no universal policy on crew flight and rest limits for its flight personnel. AR 95-1 assigns local flight commanders the responsibility of establishing flight limits. Unfortunately, in the past, attention to this problem has often resulted only after accidents have occurred, pilot and crew have reported on sick call, general mission performance was degraded or pilots reached excessively high flight hour levels.

The deleterious effect of long hours of wakefulness on a pilot's ability to fly safely cannot be resolved by a simple limitation of maximum flying hours per day or month. Although a maximum is necessary, it does not preclude the possibility that pilots who have flown fewer hours than the maximum "safe" limit are also too fatigued to make consistently sound judgments. What is required is an objective measure of fatigue which will provide an indication of the point at which performance is likely to reach unsafe levels.

This research measured various biochemical, physiological and psychological parameters that have been demonstrated previously to be related to performance or which have been shown to vary under different types of stress and compared these data with inflight performance during a period of exhaustive flight activity.

METHOD

Subjects. Ss for the present investigation were six (6) rotary wing aviators in good health between the ages of twenty-one and twenty-six. All pilots had just completed rotary wing flight school and had logged approximately 200 flight hours prior to the test.

Equipment. This research was conducted at High Falls stagefield and utilized the USAARL field test facility for housing Ss and experimenter personnel during the investigation. This facility was designed to provide living quarters and eating facilities for eight personnel and allow space for inhouse biochemical laboratory work and psychological and physiological testing.

The inflight portion of the investigation utilized the laboratory's JUH-1H helicopter and the helicopter inflight monitoring system (HIMS). This system provides data on twenty different parameters of pilot control inputs, aircraft position, rates and accelerations and aircraft status values during flight.[1] Two center fleet UH-1 aircraft were also utilized. One aircraft was used alternately for the IP check ride segments of the flight testing. The other helicopter was utilized for a reserve test vehicle, maintenance of airborne systems, and personnel and supply transportation.

Laboratory testing can be divided into four discrete categories, physiological, perceptual-motor, biochemical measures and subjective rating measures.

Physiological testing involved cardiovascular monitoring through the use of a portable Avionics EKG tape recording apparatus. These tapes were analyzed via an Avionics Dynamic Electroscanner, Model 600. Pupilometry measurements utilizing a Whittaker TV Pupilometer Model 8005 were also obtained as a measure of fatigue.

Perceptual-motor tasks utilized were a simple audio reaction time apparatus (Lafayette Model 63015) and a device designed to measure dynamic visual acuity (DVA). The apparatus used to obtain this measure was constructed specifically for the project and consisted of a combination of general experimental apparatus which allowed various sized Bausch and Lomb checkerboard targets to traverse a measured distance at various rates of speed.

Biochemical measures were obtained and analyzed from both blood and urine specimens. Various laboratory techniques and apparatus were used to separate and analyze these compounds.

Subjective data were obtained throughout the test period through the use of questionnaires. Questionnaires and subjective rating scales allowing Ss to estimate fatigue intensity, overall flight performance, and mood were provided and administered throughout the test period. Safety instructor pilots were provided with grading scales which assessed the S pilot's overall flight performance and his performance on each maneuver.

Procedures and Design. The primary aim of the study was to observe the relationship between various laboratory tests and corresponding inflight performance. In order to assess closely these relationships Ss were required to maintain a rigorous regimen of sleep-wake activity and diet. Ss were transported to the facility 48 hours prior to the first flight day and remained at the facility until the completion of the test. These first days were to familiarize them with the laboratory tasks and obtain baseline data on the physiological and biochemical parameters. Flights and testing commenced on the third day and were continued according to the schedule referenced in Table 1.

Table 1

Schedule of Sleeping, Eating, Flying and Testing

TIME FRAME	SUBJECT ACTIVITIES	EXPERIMENTAL MEASURES								
		Flight HIMS	Urine	Blood	IP Rating	Pupilo-meter	DVA	Reaction Time	Mood Scale	Fatigue Rating
0100 to 0430	Sleep Period		x							
0500 to 0600	Flight	x x x x	x	x	x					
0615 to 0800	Breakfast & Testing					x	x x	x	x	x
0800 to 0945	Flight	x x x x	x		x					x x
1000 to 1145	Flight	x x x x	x	x	x					x x
1200 to 1400	Lunch & Testing					x	x x	x	x	x
1400 to 1545	Flight	x x x x	x		x					x x
1600 to 1745	Flight	x x x x	x	x	x					x x
1800 to 2000	Supper & Testing					x	x x	x	x	x
2000 to 2145	Flight	x x x x	x		x					x x
2200 to 2345	Flight	x x x x	x	x	x					x x
2400 to 0100	Snack & Testing					x	x	x	x	x

On the first flight day, Ss were awakened at 0430 hours. Experimentation continued until 0100 hours the following day. Ss were allowed to sleep from 0100 to 0430 hours. Meals were provided to Ss at 0615, 1215, 1815 and 2400 hours. No snacks other than non-caffeine containing beverages were allowed. The consumption of alcoholic or caffeine containing beverages was not allowed, but smoking was permitted and a record of cigarette consumption was kept.

During each flight Ss were required to perform the maneuvers listed in Table 2. These maneuvers were accomplished according to a programmed schedule and graded by the Safety IP. Inflight data on selected maneuvers was also obtained. The same maneuvers program was followed by Ss flying the center fleet aircraft and each maneuver was graded by the safety pilot. The program of maneuvers was devised to preclude down time due to inclement weather. Maneuvers were accomplished up to the point in the flight where, in the safety pilot's judgment, further maneuvers could not safely be accomplished because of weather conditions. If time permitted the profile was again accomplished from the beginning.

Table 2

FLIGHT PROFILE

Bad Weather

1. 3 ft. Hover - 1 minute
2. 360° Pedal turn - left about mast
3. 360° Pedal turn - right about mast
4. Hover Taxi
5. Slope - right skid
6. Slope - left skid
7. Lateral Hover
8. 360° Pedal turn - left about nose
9. 360° Pedal turn - right about nose
10. 360° Pedal Turn - left about pilot
11. 360° Pedal turn - right about pilot
12. 360° Pedal turn - left about tail
13. 360° Pedal turn - right about tail
14. Rearward Hover

Marginal Weather

15. 10 ft Hover - 1 minute
16. 25 ft Hover - 1 minute
17. 50 ft Hover - 1 minute
18. Hover autorotation
19. Simulated max-gross takeoff
20. Traffic Pattern 300 ft AGL
    Crosswind
    Downwind
    Base
    Final
21. Shallow approach

Good Weather

22. Normal Traffic Pattern
    Crosswind
    Downwind
    Base
    Final
23. Normal Approach
24. Max performance takeoff
25. Low Level flight
    Heading
    Altitude maintenance
    Airspeed
26. Confined area landing
27. Max performance takeoff
    Heading
    Altitude maintenance
    Airspeed
28. Shallow approach

IFR (Hood)

29. Standard rate climbing turn left to 180°
30. Maintain straight and level flight 15 sec.
31. Standard rate descending turn right to 180°
32. Deceleration to 40 knots
33. Acceleration to 90 knots

Inflight Data Collection. Continuous information from twenty pilot and aircraft monitoring points were recorded for selected maneuvers during all flights. A list of these parameters is included in Table 3. This table also presents derived measures which can be obtained from the recorded parameters. Criterion values for pilot control inputs were defined in terms of control steady state, control reversal and control movement. Control steady state was defined to occur when a specified control had not exceeded an empirically defined distance in a specified time. A control reversal was defined to occur when a control changes direction and a control movement was defined as any movement starting from a steady state or control reversal and ending in a steady state or reversal. Utilizing these criteria, means were obtained for all values for magnitude, duration and rate of control movements and mean time for steady states. Frequency for steady states and control movements were also recorded. Table 4 presents the times and distances which were established as criteria delineating movement for these controls.

The distance ranges were established by determining the minimum perceived control movement for the directions of concern which were shown to yield airframe movement independent of time. Times were established by taking one-half the minimum time it took to move the various controls through the distance ranges previously established. Statistics obtained from these parameters were analyzed by Ss across all flights to determine differences in performance as a function of flight induced fatigue. Grade sheets provided to each safety pilot were tabulated and subjected to analysis. Each S's grades were compared across flights for the days of the test and differences in performance ratings were assessed.

Table 3

Parameters Measured and Derived Measures

Parameters Measured	Derived Measures
Pitch	Pitch Rate
Roll	Roll Rate
Heading	Rate of Turn
Position x	
Position y	Ground Speed
Acceleration x	
Acceleration y	
Acceleration z	
Roll Rate	Roll Acceleration
Pitch Rate	Pitch Acceleration
Yaw Rate	Yaw Acceleration
Radar Altitude	Rate of Climb
Barometric Altitude	Rate of Climb
Airspeed	
Flight Time	
Rotor RPM	
Throttle	
Cyclic Stick (Fore-Aft) (CYCFA)	Control Position, Absolute Control
Cyclic Stick (Left-Right) (CYCLR)	Movement Magnitude, Positive Control
Collective (COLL)	Movement Magnitude, Negative Control
Pedals	Movement Magnitude, Absolute Average Control Movement Rate, Average Positive Control Movement Rate, Average Negative Control Movement Rate, Control Reversals, Instantaneous Control Reversals, Control Steady State, Control Movement.

Table 4

Baseline Times and Movement Limits for Controls

	CYCFA	CYCLR	COLL	THROTTLE	PEDAL
Time duration in seconds	.25	.15	.45	.50	.50
Movement limits in inches	.37	.32	.35	.50	.35

Biochemical Analysis. Urine samples were collected after awakening and at three hour intervals starting at 0600. Samples were acidified within 10 minutes of collection, frozen immediately at -100°C in an ethanol base and stored at -70°C until analyzed. Analysis included creatinine, epinephrine, norepinephrine, corticoids, and lactic acid.

Blood samples were collected twice daily via venapuncture at 0600 and 1800 before eating. Analysis of whole blood included pH, pCO_2, pO_2, hemoglobin, hematocrit, differential leucocyte count and lactic acid. Serum and heparinized plasma were prepared, immediately frozen and stored at -70°C until analyzed. Plasma was analyzed for cortisol. Serum was analyzed for uric acid, cholesterol, triglycerides, SGOT, LDH, CPK, iron, glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, total protein, albumin, alkaline phosphatase and total bilirubin.

Physiological Monitoring. Electrocardiographic data was obtained continuously during waking hours over the entire period of the experiment. Average heart rate and rate of variation was of primary interest. EKG data was also obtained and is available for inspection. Pupilometer measurements were made four times daily according to Table 1. The measurements include pupil responses to light stimuli and pupil diameter changes during a 15 minute period of darkness.

Perceptual Motor Testing. During control day and each flight day Ss were required to have their DVA assessed as referenced in Table 1. Five different sizes of checkerboard targets were used for which the angular size of critical detail varied from 1.3' to 2.8'. Target luminance was approximately 37 fL, background 1.1 and contrast 84%. Ss were required to resolve and respond to each target at sweep times of 25° and 40°/sec. Each session consisted of random presentations of a combination of three orientations of the target and five different target sizes. Thirty trials were administered per session. Data for all Ss were tabulated and plotted across days and by time of day. Comparisons of DVA performance, flight performance ratings and fatigue intensity were accomplished.

Audio reaction time data were obtained in four sessions each day. Response latency times for 100 reaction time trials per session were collected and an analysis of variance was accomplished to assess performance differences across days and sessions.

Subjective Measures.

(a) Overall Flight Performance (1) - Estimations of overall flight performance were obtained from both Ss and safety pilots after each flight. The questionnaire used to obtain this information was modeled after the Cooper - Harper pilot rating scale discussed by Helm.[2] Each S and safety pilot selected a number from the scale which in his opinion most closely described the S's performance on the mission he had just completed.

(b) Overall Flight Performance (2) - Ss also estimated the overall flight efficiency by a second means. This simple technique required Ss to place a single mark on a line of standard length. The position of this mark was used to indicate goodness of flight performance. This scale has been described by Hartman et al.[3]

(c) Ss were also rated by their respective safety pilots on each maneuver they performed during the mission. A simple scale of 1 to 10 was used with five representing average performance.

(d) Fatigue Intensity - The standard line technique referenced in (b) was also used to obtain measure of subjective fatigue intensity. Before and after each flight Ss were required to estimate the degree of fatigue felt by this means.

(e) Feel Tone Checklist - Another means of assessing fatigue intensity utilized during the test was a modified feeling tone checklist modeled after Pearson and Byars.[4] This scale consisted of a list of adjectives with corresponding response categories of better than (0), same as (1), worse than (2) Data from this measure was coded by assigning numbers to the three response categories and obtaining totals for the responses on each questionnaire, higher numbers corresponding to negative responses. This scale was not completed after every flight but corresponded more closely to the laboratory task schedule as listed in Table 1.

(f) Mood Checklist Scale - Similarly, a scale assessing mood changes over time was administered. This scale is discussed in detail by Radhoff and Helmreich.[5]

These subjective measures were tabulated and analyzed with respect to each other, inflight data, laboratory task data and biochemical findings.

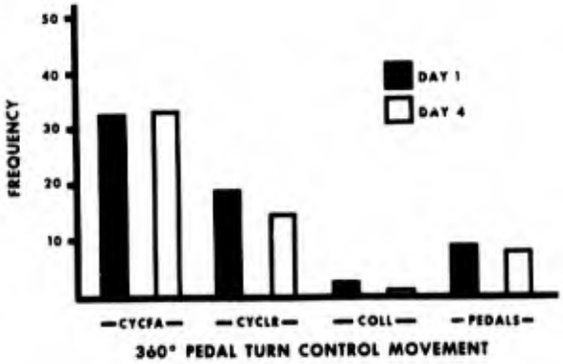
RESULTS

Due to limitations on space, only representative data on various categories of information collected will be presented in this report. In-flight data from flights on Day 1 and Day 4 were compared for three maneuvers to include a 360° left pedal turn about the mast, a 50 foot high hover, and a rearward hover. The maneuvers are judged to be reasonably difficult to perform with precision and it was postulated changes in the degree of proficiency in performing them would possibly be reflected by time at task, and resultant fatigue affects.

The 360° pedal turn required the aviator to bring the aircraft to a three foot hover, and maintaining constant position, provide the necessary control to pivot the aircraft about the mast for 360°, returning to the start heading.

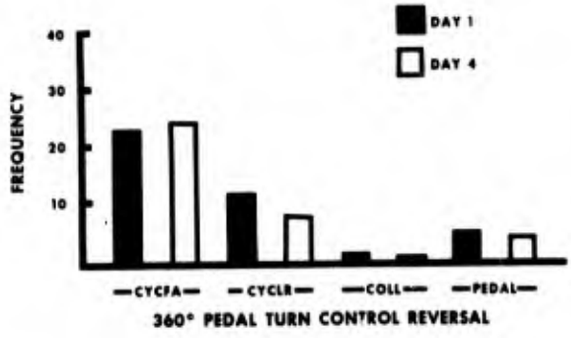
In assessing control input parameters for the 360° pedal turn, it was found that in almost all control categories a decrease in activity was noted between Day 4 and Day 1.

Figure 1 depicts the mean frequency of control movements across sessions for Day 1 and Day 4. It can be noted that with the exception of frequency of CYCFA movement which has equivalent figures for both days, less movement was found for other control parameters. These same trends are present for mean frequency of control reversals as referenced in Figure 2. It can be seen that with the exception of a slight increase in the frequency of CYCFA reversal activity on Day 4, all other parameters are shown to decline between days.



360° PEDAL TURN CONTROL MOVEMENT

FIGURE 1

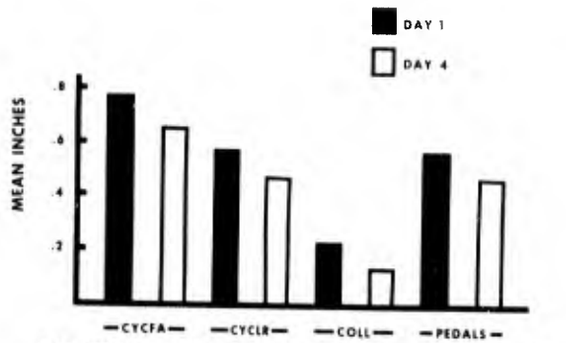


360° PEDAL TURN CONTROL REVERSAL

FIGURE 2

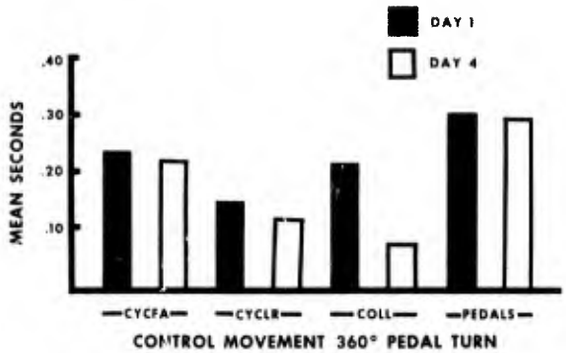
Control movement magnitude was also found to be less for Day 4. This trend is reflected in Figure 3. For all control categories, the relative size of control movements became smaller as a function of time at task.

Control movements were also found to be of shorter duration for Day 4 than Day 1. Figure 4 illustrates this trend.



360° PEDAL TURN ABSOLUTE CONTROL MOVEMENT MAGNITUDE

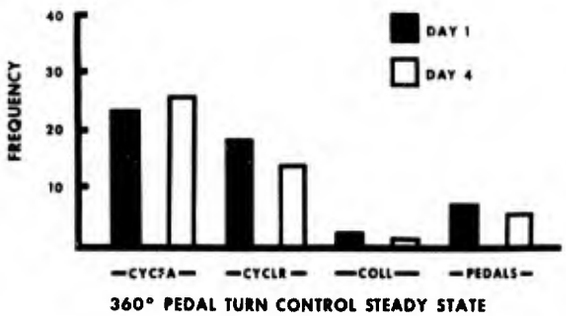
FIGURE 3



CONTROL MOVEMENT 360° PEDAL TURN

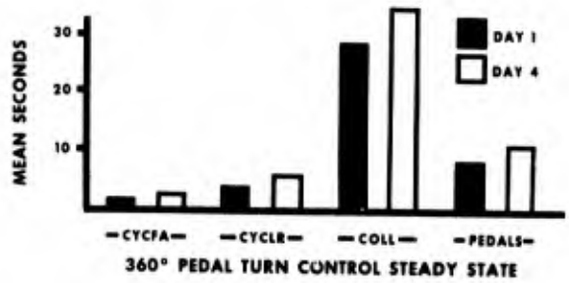
FIGURE 4

Since control activity as referenced above was found to decline from Day 1 to Day 4, it would be expected that considerably more control steady state periods would be found for these control parameters during the 360° turn maneuver. This was not the case. Mean frequencies of CSS are plotted for the two days in Figure 5. It can be seen that with the exception of CYCFA the number of control steady states decreased from Day 1 to Day 4. However, the period of time that aviators spent with their controls in a steady state did increase. Figure 6 shows an increase in the mean duration of steady state times for all control parameters.



360° PEDAL TURN CONTROL STEADY STATE

FIGURE 5



360° PEDAL TURN CONTROL STEADY STATE

FIGURE 6

Figure 7 is a composite graph of the percentages of flight time spent in movement and steady state for the four control parameters.

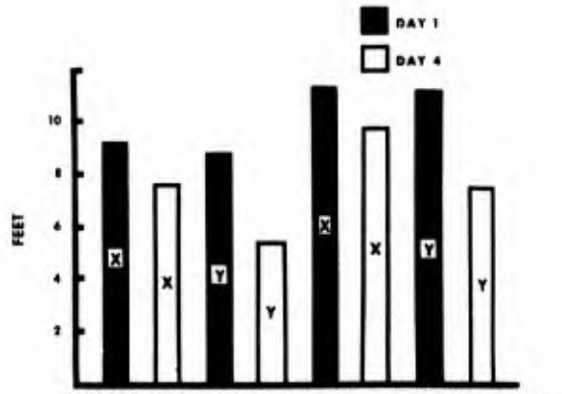
Note that a lesser percentage of time was spent in Cyclic FA-LR activity on Day 4 than Day 1. Based on other measures of these two parameters, it can be stated that this activity was reflected in slow, small and relatively smooth control movements, exhibiting finer control with little over-control responding. Pedal and collective movement percentages on this measure demonstrate discrete control inputs with considerable periods of steady state. This could be evidenced as aviator responding only when changes in these parameters are absolutely vital for the accomplishment of the specific maneuver.

For the 360° Pedal Turn, it appears that aviators decreased their physical activity as a function of fatigue while allowing only control movements of a size and duration necessary for adequate aircraft control and maneuver performance. No excess activity was exhibited because of the resultant physiological cost.

Surprisingly, this approach created better performance for this maneuver. Figure 8 depicts a plot of position error (average absolute error; root mean squared error) in X and Y coordinates for this maneuver. It can be noted that error in both X and Y decreased from Day 1 to Day 4.

360° PEDAL TURN TOTAL FLIGHT TIME CONTROL STEADY STATE CONTROL MOVEMENT

FIGURE 7



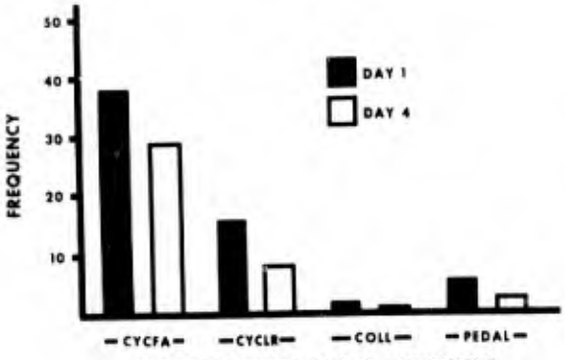
360° PEDAL TURN X AND Y DEVIATION

FIGURE 8

The 50 ft hover maneuver required the aviator to bring the aircraft off the ground to the altitude he considered to be fifty feet above the terrain and maintain the aircraft at that position, heading and altitude for one minute. This maneuver required the aviator to perceive and correct for drift in position and altitude changes, monitor critical instruments for engine status as well as maintain precise aircraft control.

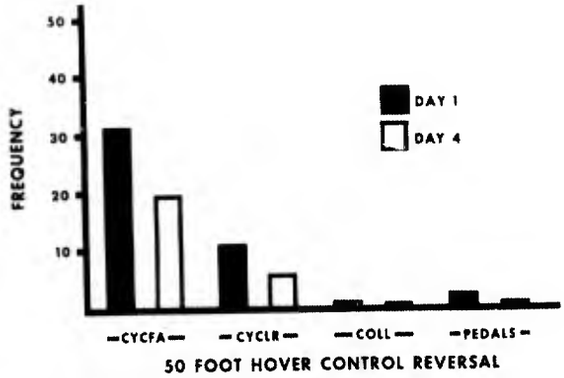
Similar trends in control activity as referenced for the 360° Pedal turn are reflected for the 50 foot hover maneuver. Frequency of control movements for the 50 foot hover are shown in Figure 9. Note the decrease in control activity as reflected by number of movements during the maneuver for all controls from Day 1 to Day 4.

Mean frequency of control reversals also demonstrate a similar trend. Figure 10 illustrates the change in the number of control reversals between days.



50 FOOT HOVER CONTROL MOVEMENT

FIGURE 9

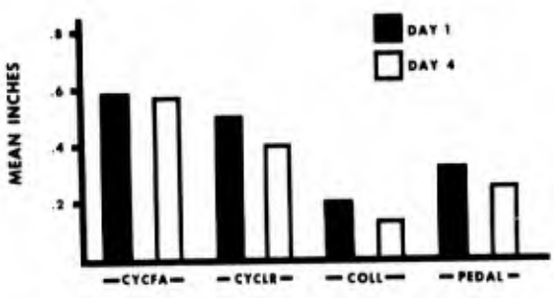


50 FOOT HOVER CONTROL REVERSAL

FIGURE 10

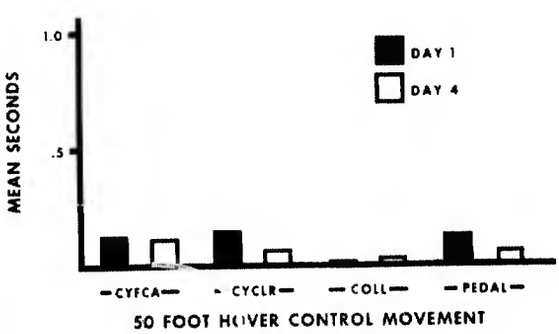
Again, as with the 360° Pedal Turn maneuver, Absolute Control Movement magnitude decreased from Day 1 to Day 4. Subject aviators made considerably smaller control inputs on the average for this maneuver on the latter flight day. Figure 11 illustrates this trend.

In a similar manner, the length of time for control movements decreased from Day 1 to Day 4. Subject pilot's control movements were of shorter duration as a function of time at task as referenced in Figure 12.



50 FOOT HOVER ABSOLUTE CONTROL MOVEMENT MAGNITUDE

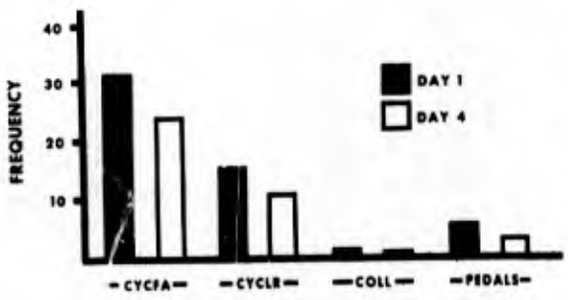
FIGURE 11



50 FOOT HOVER CONTROL MOVEMENT

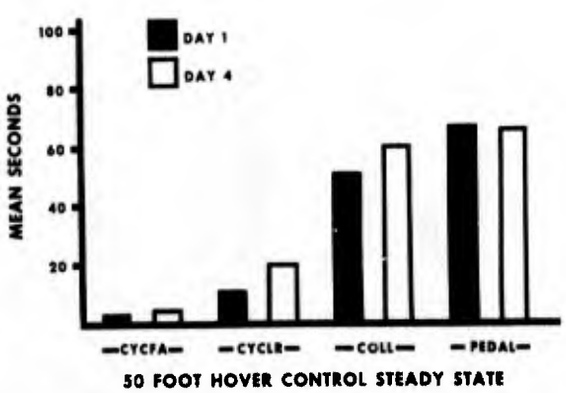
FIGURE 12

The number of control steady states also decreased across days for this maneuver as referenced in Figure 13. However, the length of time for each control steady state period was found to increase across days as was the case for the 360° Pedal Turn maneuver. This trend is depicted in Figure 14.



50 FOOT HOVER CONTROL STEADY STATE

FIGURE 13

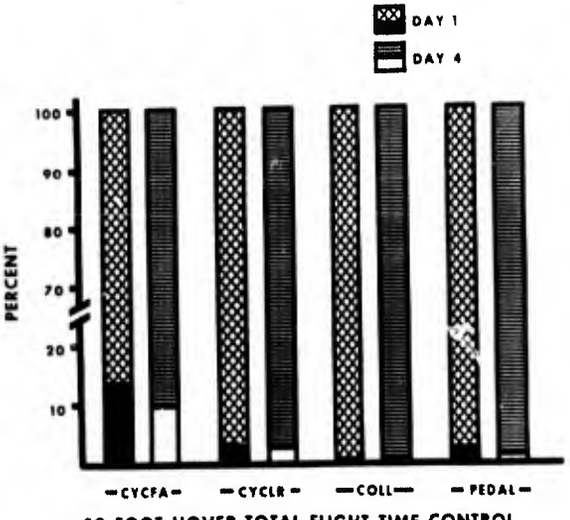


50 FOOT HOVER CONTROL STEADY STATE

FIGURE 14

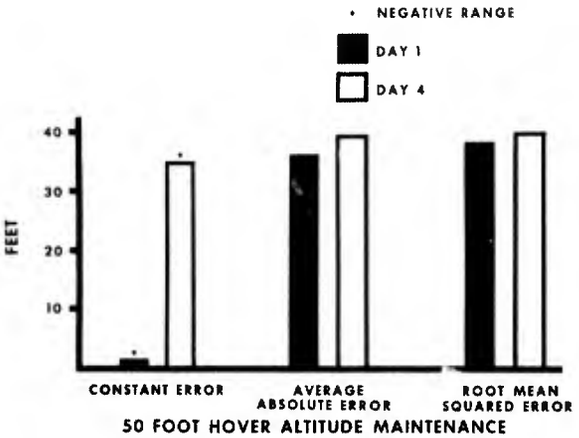
A composite plot of the percent of total flight time spent in steady state and movement for all control parameters is shown in Figure 15. This graph illustrates that pilots exhibited less control activity as a function of time at task for this maneuver as they did with the 360° pedal turn.

As illustrated by the previous data a decrease in control activity was evidenced between flight days. However, unlike the 360° pedal turn maneuver, data from the 50 foot hover did reflect a trend in the direction of flight performance decrement as a function of time at task. For example, it seemed more difficult for Subject aviators to select and maintain the 50' altitude on day 4 as opposed to day 1. Figure 16 presents constant error, absolute error and RMS error in feet for this maneuver. Note that negative constant error, absolute error, and RMS error show an increase from Day 1 to Day 4. Although absolute error decreased slightly for Day 4, reflecting the trend of less overall error, it is of interest to note that the constant error measure reflects a predisposition for S aviators to select and maintain altitudes lower than criterion height. RMS error scores reflect increased variance in performance as compared to the mean altitude flown regardless of criterion attitude. Thus, aviators seemed to have more difficulty in selecting the 50' hover altitude as well as maintaining their altitude once selected.



50 FOOT HOVER TOTAL FLIGHT TIME CONTROL MOVEMENT STEADY STATE CONTROL

FIGURE 15



50 FOOT HOVER ALTITUDE MAINTENANCE

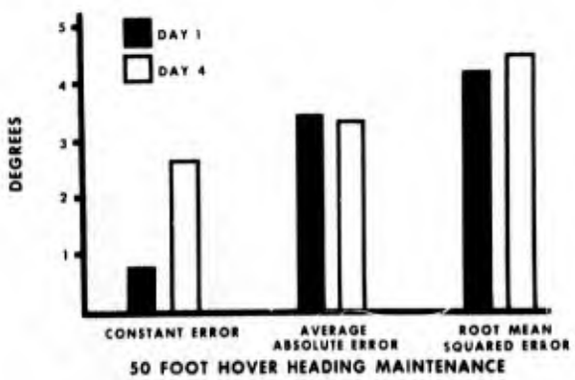
FIGURE 16

Heading maintenance was also more difficult for S on Day 4 as referenced by Figure 17. Although the tendency to maintain a heading to the right of criterion was evident for day 1 this tendency was seen to increase for day 4. Overall absolute error, that is amount of error for the maneuver was slightly lower for day 4 but variability about mean heading maintained was slightly larger for the latter flight day.

Control parameter data presented for the 50 foot hover maneuver seem to reflect decreased activity as a function of physiological cost, similar to the 360° pedal turn maneuver. Trends in error data while not conclusive seem to indicate some performance impairment for day 4.

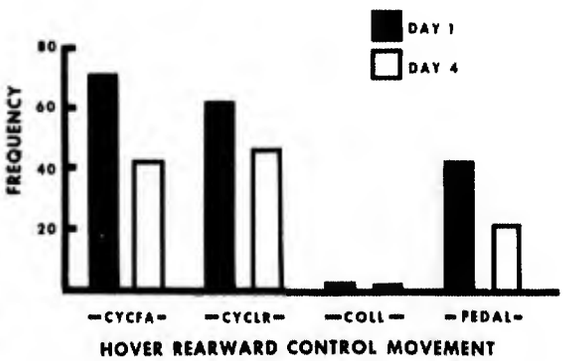
The rearward hover maneuver required the S aviator to bring the aircraft to an altitude of 3 ft AGL, hover taxi the aircraft rearward to a predetermined point using the center line of the runway as a visual reference. This maneuver required precise control input, heading maintenance and ground track.

As with the two previously discussed maneuvers S aviators demonstrated a decrease in frequency of control movement between Day 1 and Day 4. Figure 18 illustrates this trend.



50 FOOT HOVER HEADING MAINTENANCE

FIGURE 17

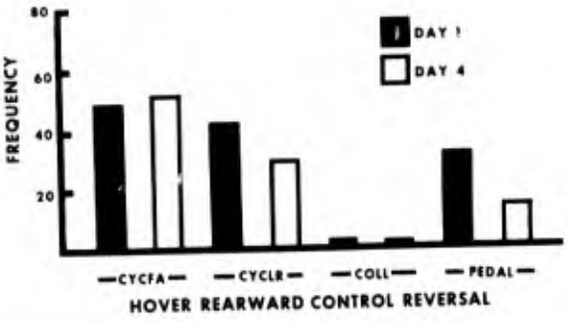


HOVER REARWARD CONTROL MOVEMENT

FIGURE 18

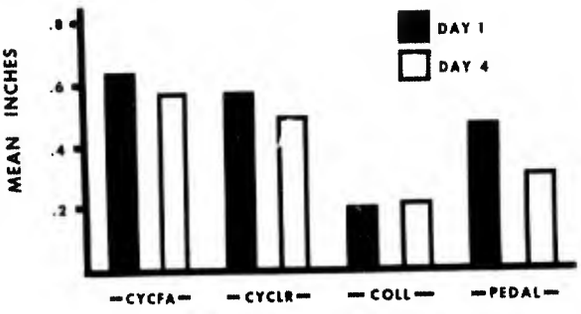
Similarly with the exception of a slight increase in CYCFA activity, this trend is also in evidence for the frequency of control reversals for this maneuver as shown in Figure 19.

Average absolute control movement magnitude was also found to decrease for Day 4 flights. Figure 20 depicts this trend, with the exception of collective control which stayed relatively stable between days.



HOVER REARWARD CONTROL REVERSAL

FIGURE 19

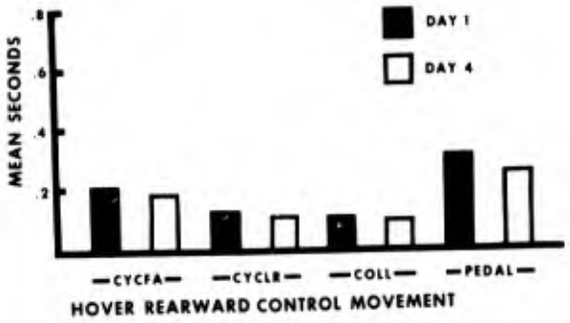


HOVER REARWARD AVERAGE ABSOLUTE CONTROL MOVEMENT MAGNITUDE

FIGURE 20

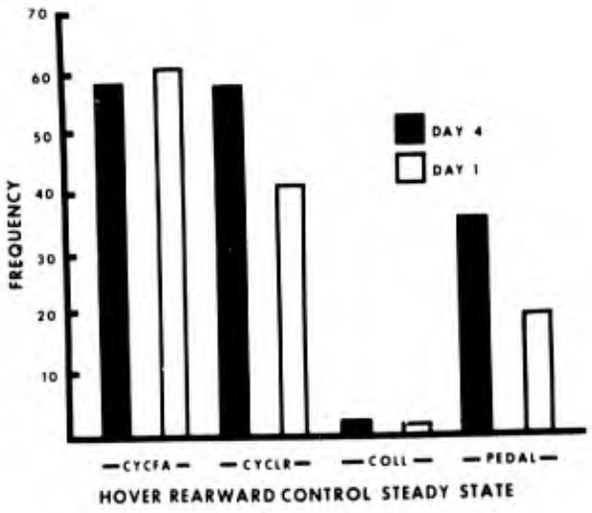
The mean duration for control movements also illustrate this trend. Figure 21 represents these data for Day 1 and Day 4. It is of interest to note that these differences are not very large, thus demonstrating that the control response requirements of this maneuver are relatively constant and were not subject to voluntary change by aviators.

The mean frequency for control steady state is illustrated in Figure 22. Except for slightly less CYCFA activity reflected by more control steady states for this measure, the number of steady state periods decreased from Day 1 to Day 4. The mean duration of these steady state periods, however, increased.



HOVER REARWARD CONTROL MOVEMENT

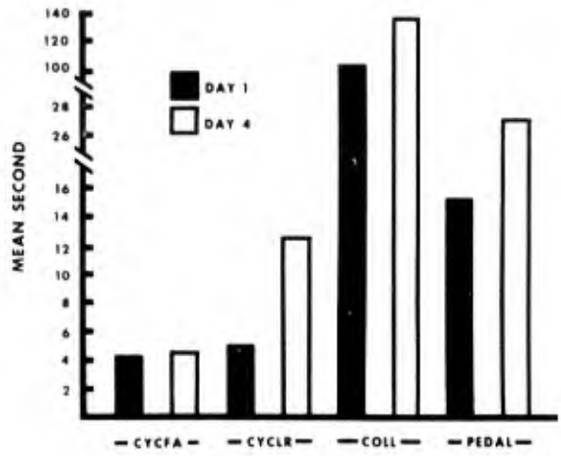
FIGURE 21



HOVER REARWARD CONTROL STEADY STATE

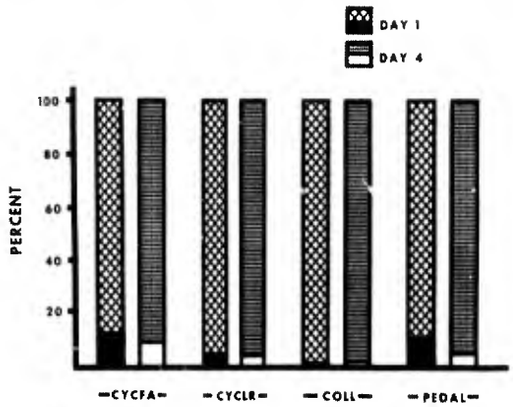
FIGURE 22

Figure 23 presents a plot of the mean duration of control steady state times for the rearward hover maneuver. Figure 24 is a plot of the percentage of total flight time spent in control steady state and control movement. In noting the proportions of time spent in control activity, it can be observed that there was a slight increase in cyclic FA activity between the two flight days but all other measures showed decreased control responses on the latter flight day.



HOVER REARWARD CONTROL STEADY STATE

FIGURE 23



HOVER REARWARD CONTROL STEADY STATE CONTROL MOVEMENT

FIGURE 24

As with the 360° pedal turn and 50 ft hover maneuver, control activity for the rearward hover generally decreased as a function of time at task. This decrease was reflected by larger periods of steady state and fewer, shorter, and smaller control movements. This change was demonstrated for all maneuvers with very little evidence of change in flight performance efficiency.

In considering the inflight performance results for the three maneuvers presented, the trends in performance would possibly indicate better pilot proficiency as a function of time on the task. However, this hypothesis does not seem to have much merit in light of other in-house laboratory measures. Although subjects did not view their performance to be much worse on Day 4 than on Day 1 and their performance as rated by their IP safety pilots also demonstrate this trend, subjective measures of fatigue and laboratory tasks assessing performance as a function of fatigue show a decided negative trend across days.

Biochemical Measures. The experiment offered the opportunity to examine circadian variations in numerous blood and urine components and chemical parameters. Urine analyses were particularly interesting since sampling was frequent and continuous over the entire experimental period. It was possible to detect phase as well as amplitude changes in the diurnal patterns. An example of the changing urine pH pattern for pilot #3 is shown as Figure 25. This figure demonstrates a consistent increase in daily pH maximum (0900) that was observed in all pilots during the latter flight days. It can also be noted that for this pilot the secondary rise in pH at 2100 is diminished by the fifth flight day and reappears on the second post-control day.

The causes for the changing diurnal pH pattern are not known. Food ingestion, physiological activities and water diuresis are all factors which are known to influence pH. Eating patterns in the experiment were consistent and would not be expected to cause the changes observed. The reduction in exercise during the flying days may account for part of the difference as well as the increased urine volume that was frequently associated with higher pH values.

The most consistent change in the blood chemistry analysis was observed for serum calcium (Figure 26). In all subjects, the calcium level was highest during flying. The increase in serum calcium may have important implications in the mineral metabolism of helicopter pilots since other work with experimental animals has indicated that exposure to vibrations may either induce bone mineral depletion or enhance bone remodeling depending on the frequency of vibration.[6] The reduced mobility of the pilots in the cockpit environment may also be a factor since it is known that immobilized bones have a greater responsiveness to parathyroid hormones than active bones. The known effects of steroid hormones on bone calcium, intestinal calcium absorption and kidney tubular resorption may also be important. However, further studies are necessary to determine the effects of extensive helicopter flight operations on the long term mineral balance of pilots.

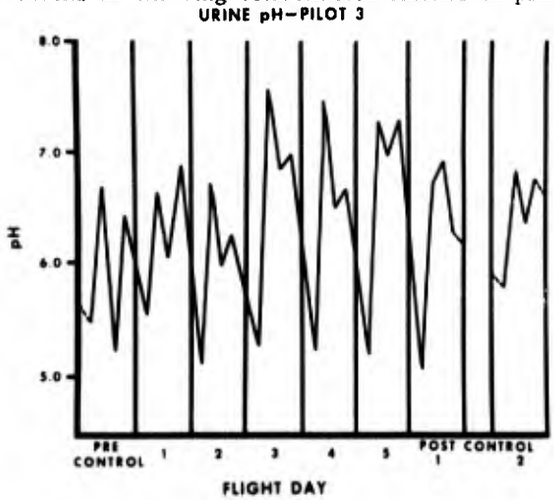


FIGURE 25

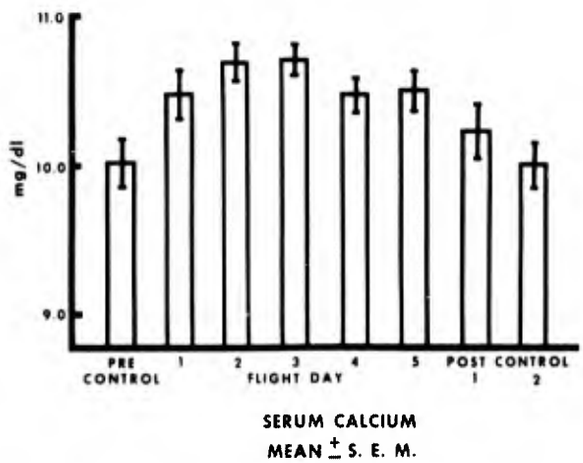


FIGURE 26

DVA Performance. Representative data on the DVA task for a single subject is presented in Figure 27. Mean target thresholds in minutes of arc are plotted for each session across days. Note the improvement with practice the first control and first flying day. This is followed by considerably poorer performance during the next flight days with much but not consistent diurnal variation. After the full night's sleep at the end of the flight section of the test, DVA performance is very good, as it is on the control recovery day.

These trends are shown for the last four pilots as a group in Figure 28.

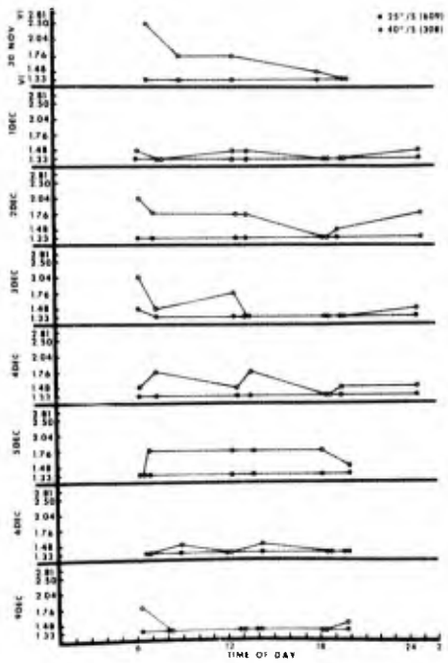


FIGURE 27

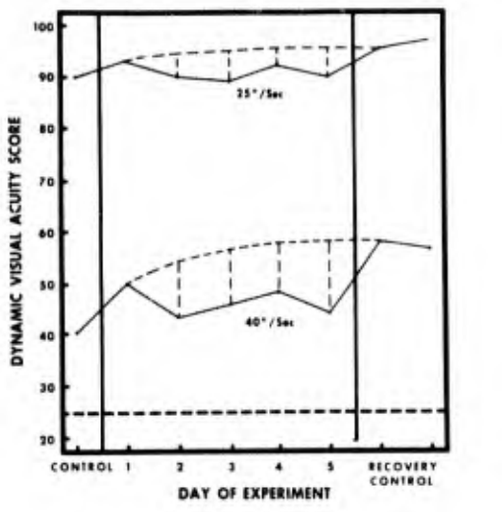


FIGURE 28

The solid curve depicts the mean DVA performance, while the dashed curve portrays a hypothetical DVA practice or learning curve in the absense of fatigue. The difference in the two curves is an estimate of DVA decrement with fatigue. Difference in DVA scores over days were significant at less than .02 level for 40°/second and approached significance at 25°/second. ($\alpha \simeq .065$)

These DVA scores were compared to both the subjective fatigue intensity and S pilot's and safety pilots' estimates of flight performance. The mean ratings for fatigue intensity are shown in Figures 29 and 30.

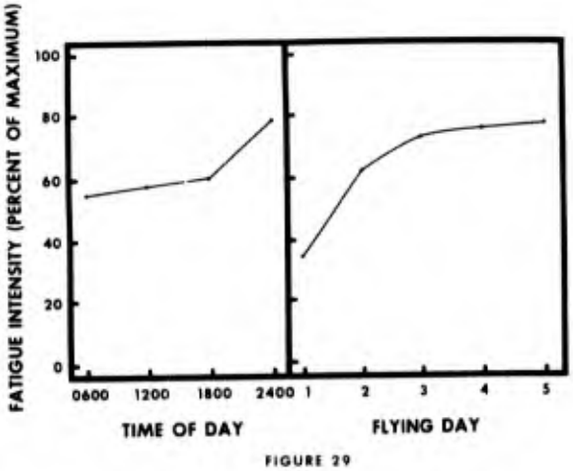


FIGURE 29

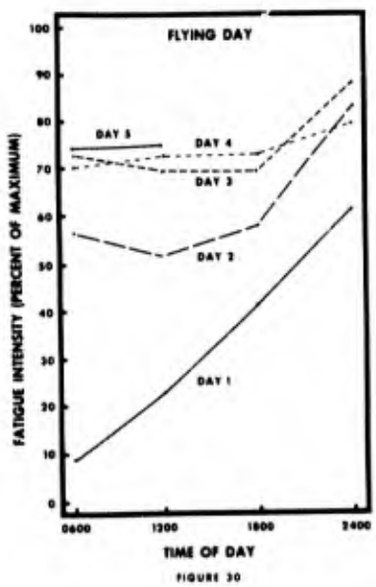


FIGURE 30

It can be seen that over the five flight days, fatigue ratings increased gradually during the day and then rapidly at night. They also increased rapidly the first day or two and gradually thereafter.

In spite of an obvious buildup of fatigue over flying days, pilots did not assess their flying performance to be impaired and this is corroborated by the objective inflight performance data and ratings of their safety pilots. Mean ratings for Ss and safety pilots are presented in Figure 31.

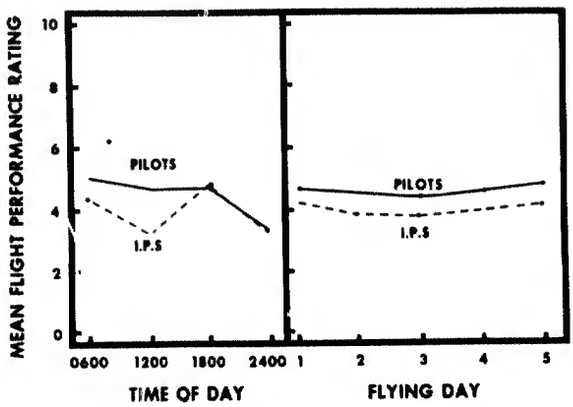


FIGURE 31

There is some diurnal variation, in the pilots' ratings of their own performance, as referenced by a gradual decline at night, mirroring their fatigue assessment.

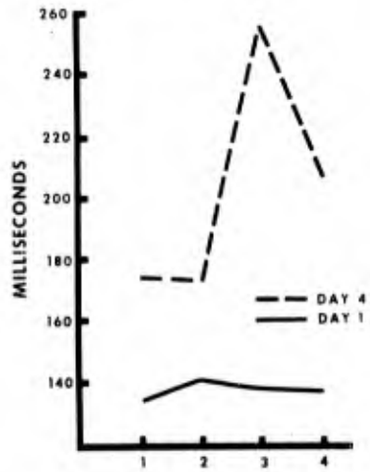
The correlations between DVA and the various measures previously described are listed in Table 5. In the first row are the correlations between ratings of fatigue intensity obtained in the aircraft at the end of each flying session and the DVA score obtained a few minutes later. The correlations are based on 18 pairs of measures, and while negative as expected for 3 of 4 Ss, the r is significant only for S4. Similarly, the correlations obtained from Fatigue Intensity rating and DVA after meals are mostly negative with one (S6) reaching significance. All correlations between flying performance ratings and DVA are positive although relatively low.

Table 5

Correlations: DVA and Subjective Fatigue and Performance Ratings

	SUBJECT			
VARIABLES	3	4	5	6
FI (Aircraft)/DVA pre	-.23	-.42	.15	-.18
FI (Bldg)/DVA post	-.24	.33	-.17	-.48
FP/DVA pre	.50	.17	.32	.32
FPR-Ss/DVA pre	.19	.30	.22	.20
FPR-IP/DVA pre	.34	.39	.08	.33
FPR-IP 1st hr/DVA post	.32	.11	.48	.20

Audio Reaction Time. Audio Reaction Time data was tabulated for all Ss for the four daily sessions for Day 1 and Day 4 and submitted to an analysis of variance. Significant variation across days ($F = 12.864$, df 1 and 5) were demonstrated. Increased mean latency response times are plotted for these days in Figure 32.



-AUDIO REACTION-
MEAN RESPONSE LATENCY TIMES BY SESSIONS

FIGURE 32

Note the large differences in response latency between the two days as well as the variability between sessions. This variability is especially prevalent for Day 4 with an exceptionally large mean latency time evident for session 3. The time of this session corresponds to 1800 hours which when compared with the fatigue intensity data for that period shows an increased amount of fatigue at this time of day.

Pupillometry. Previous investigators have studied the wave form characteristics of pupillary reflex response to light and have shown that there is an irregular relation between the shape of the pupil size and various light stimulus intensity levels.[7,8] Further work by these and other scientists have led to the assumption that the wave form characteristic of pupillary reflex response to light may be an objective evaluation of fatigue. On the basis of this postulate, data consisting of pupillary responses to light stimuli during the two daily experimental sessions were obtained and assessed. Figure 33 is a plot of representative data for one subject on Day 1 and Day 4. It is evident that pupillary reflex response waves are relatively smooth for Day 1 in contrast to the fourth flight day. For data on other Ss, flat bottomed, W shape wave forms were also common for Day 4. Similarly, it is interesting to note the longer latency recovery times for Day 4. From preliminary observation, these data seem to indicate consistant irregularities in pupillary response as a function of fatigue.

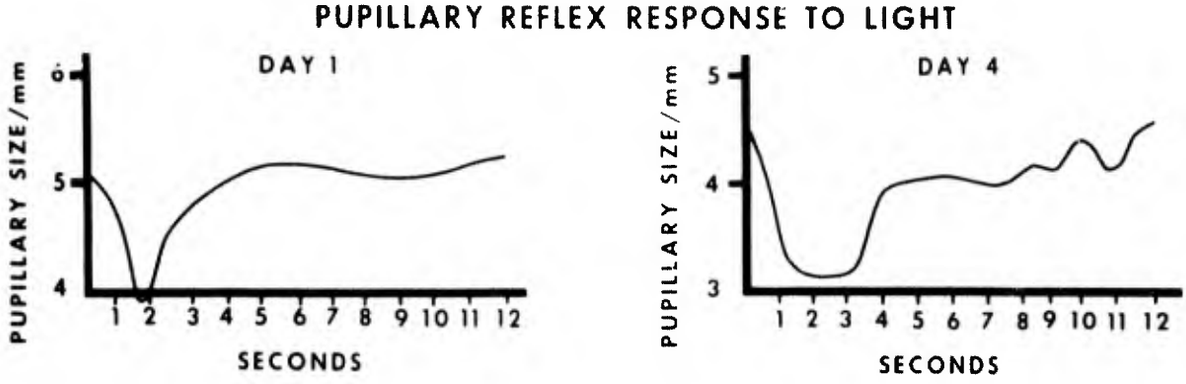


FIGURE 33

Feeling Tone. Responses from the feeling tone checklist are plotted in Figure 34, for the five flight days and control and recovery days. These results seem to illustrate a trend similar to that found for fatigue intensity in that there was a sharp decrease in Ss' estimation of physical well being between the control day and first day of flight with a gradual increase thereafter until the recovery day. These data also agree closely with trends found for the data obtained on the reaction time task and results obtained for DVA performance.

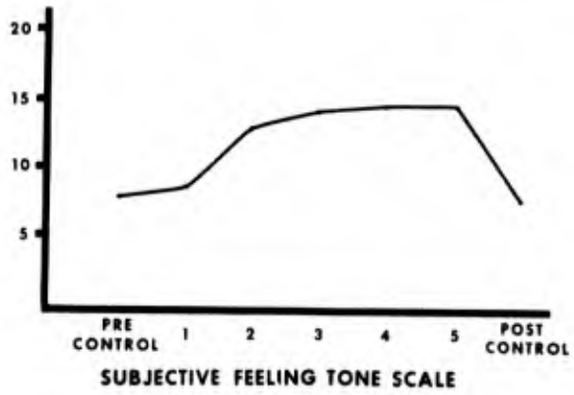


FIGURE 34

DISCUSSION

Classic literature with regard to the effect of sleep loss and continuous task operation would indicate that a decrement in performance would be demonstrated as a function of fatigue. Preliminary observation of data collected on various in-house tasks, biochemical parameters and subjective questionnaires during this investigation would seem to parallel this trend. For example, reaction time data was seen to demonstrate significant increased response latency times between Day 1 and Day 4, as well as variations in response latencies between sessions on both flight days. DVA performance also emulates this trend, with considerable performance decrement across flight days as compared to control day data and rapid recovery in DVA performance after sleep. Subjective measures of fatigue intensity increased across flight days and adequate recovery was evidenced for post control day measures.

Flight data, however, provides a somewhat different picture in that performance decrements on some parameters, although present are not consistant. For the three maneuvers discussed, error data was only found to follow a negative trend for the 50 foot hover maneuver. The decrease in control activity across flight days is not surprising. Helicopter pilotage under normal conditions, is typically viewed by aviators to be a task where continuous control responding is necessary for correct maintenance of aircraft flight. In adopting this philosophy, aviators typically exercise more and larger continuous control inputs than are necessary for adequate flight maintenance, the result being a situation where over-control and subsequent corrections to this control is continuously taking place. It can be hypothesized that in the case of the fatigued aviator, the physical cost of this typical control behavior becomes so great that over-control activity ceases and only responses to perceived changes in correct aircraft response are elicited. That is, only when the aircraft is judged to be out of the subjective tolerances required by the maneuver being performed will the fatigued aviator make a corrective response. Although this approach would seem

to be in contrast with the requirements of rotary wing flight owing to the reputed instability of this type of aircraft, these data would indicate that aircraft performance can be adequately accomplished with this type of control responding.

Subjective post-test interview data from S aviators and safety pilots would support this interpretation. Upon questioning, all aviators stated that muscle fatigue as evidenced by notable soreness and cramps became so great on the latter flight days that it became increasingly difficult to move their limbs to make necessary control responses. For example, a primary complaint which was registered was that the center fleet aircraft used in the test had an extremely stiff collective control and in the latter flight days, Ss were constantly frustrated by the amount of physical effort they had to expend to bring that particular aircraft to a hover. Another major complaint was lower back pain radiating to the upper torso, i.e., shoulders and neck as the testing progressed. S aviators felt that this was the reason that the majority of them deleted their scan of instruments on takeoffs and landings and failed to continue to clear the aircraft for hovering pedal turns.

Safety pilot statements with regard to S aviator performance support these data. It was their opinion that although the performance of specific maneuvers did not differ to any appreciable extent across days; all Ss became slower, failed to consistently use proper safety procedures and were less willing to proceed from one maneuver to another according to the required schedule. Safety pilots also were of the opinion that many emergency situations which could have been encountered during flight may not have been perceived by S aviators in time for them to exercise correct judgment and initiate proper control responses. In considering both objective inflight performance data and subjective S and safety pilot opinion, it must be observed that although the primary task of piloting the aircraft was not demonstrated to deteriorate as a function of fatigue, numerous deficiencies were observed in performing secondary tasks as previously described. This phenomena of primary task responding at the cost of secondary task performance degradation has been demonstrated by past laboratory research.[9,10,11,12] Flight research conducted by Billings, et al[13] has also demonstrated similar findings. Although this investigation utilized alcohol as the stressor rather than continual task performance and sleep loss, Ss were found to attend to the primary task of aircraft pilotage, while committing procedural errors similar to those observed for the present S group.

The preliminary findings of this research effort must be interpreted with caution. As referenced in Table 2, numerous other maneuvers were flown and the data obtained has yet to be analyzed. It is possible to assume that the previously discussed maneuvers did not provide as adequate a measure of performance variability as others still to be assessed. Similarly, performance effects of flight induced fatigue may be present prior to the start of Day 4 testing. Future work will provide these answers.

With reference to the primary aim of this research, that of determining in-house measurement techniques which will aid in the prediction of flight performance as a function of fatigue, several tasks look promising. Future efforts will be directed at obtaining data for these measures which can be utilized to refine and validate their predictive capability.

DISCLAIMER

The findings in this report are not to be construed as an Official Department of the Army position unless so designated by other authorized documents.

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STUDIES ON STRESS IN AVIATION PERSONNEL: ANALYSIS AND PRESENTATION OF DATA DERIVED FROM A BATTERY OF MEASUREMENTS

C. E. Melton, J. M. McKenzie, J. T. Saldivar, and Marlene Hoffmann
Aviation Physiology Laboratory, Civil Aeromedical Institute
Federal Aviation Administration, P.O. Box 25082
Oklahoma City, Oklahoma 73125

SUMMARY

Total stress in working people can be understood only through a battery of measurements that give insights into the function of several systems. When personnel are piloting aircraft or controlling air traffic, the measurements must be made on easily obtainable fluid--usually urine--so that the task is not compromised. Adrenal steroids are primarily reflective of chronic stress, whereas the catecholamines are related to acute stressors. Narrative descriptions of changes in excretion of stress indicators are difficult to follow. Because of complexity of data from batteries of measurements, the usefulness of stress studies is largely denied to managers.

A method has been devised whereby data related to stress indicators are weighted so that their importance is equivalent. The weighted values are integrated to yield an index, C_g, which allows a comparative overview of stress in air traffic control facilities. Data so normalized can be presented in graphic form without oversimplification.

An appreciation of total stress in working people can be gained only through a battery of measurements that give insights into the functional status of several organ systems. This is true because stressors of different qualities evoke primary responses from different organ systems. The effluents from these systems cannot readily be tapped close to their sources via venipuncture when the personnel under study are performing critical tasks, such as piloting aircraft or controlling air traffic. The measurements must be made on some easily obtained material--usually urine--so that performance of the task is not compromised.

Adrenal cortical contribution to the stress response is assessed through measurement of the amount of 17-ketogenic steroids (st) in the urine. The 17-ketogenic steroids closely reflect the functional state of the adrenal cortex and resemble the 17-hydroxycorticosteroids, which also closely reflect adrenal cortical function. Some authors refer to the 17-ketogenic steroids as "total 17-OHCS." The 17-ketogenic steroids include those compounds, principally the 17-OHCS, that form 17-ketosteroids upon oxidation with sodium periodate. The pre-existing urinary 17-ketosteroids (in males, these are primarily of gonadal origin) are destroyed by reduction prior to this final oxidation.[1] Adrenomedullary function is assessed by the measurement of urinary epinephrine (e).[2] Small quantities of e are formed by chromaffin tissue other than the adrenal medulla, but the amounts are not a significant fraction of the e excreted in the urine.

Sympathetic nervous system function is assessed by the amount of urinary norepinephrine (ne).[2] Norepinephrine is normally methylated in the adrenal medulla to form epinephrine, and little ne is secreted by the adrenal medulla except under extreme conditions that cause depletion of medullary epinephrine. In urine there is normally 2 to 10 times as much ne as e, and essentially all of the ne comes from sympathetic nerve terminals.

In air traffic controllers, st levels are primarily indicative of chronic stress arising from ongoing situational conditions, such as labor-management disputes, marital difficulties, or any other unresolved conflicts. Catecholamine excretion reflects primarily acute stress generated by workload, anxiety, excitement, or physical exertion. Epinephrine excretion is more closely related to the air traffic workload than is ne.

Narrative descriptions of changes in excretion levels of these three substances under different conditions become extremely complicated and are difficult to follow. The level of complication is increased when changes in the excreted amounts of these substances in different populations are being compared. Because of the complexity of data from batteries of measurements, the usefulness of objective stress studies is largely denied to the managerial people most in need of such information.

A simple method has been devised in the Aviation Physiology Laboratory for integrating the measurements of the three urinary stress indicators (st, e, and ne) into an index.[3] In the calculation of this index, resting and working values for the three individual stress indicators are treated so that the importance of each is equally weighted in the final composite stress index. The resting values are determined from the urine formed during nocturnal sleep. The working values are derived from all the urine formed and excreted during an 8-hour work period.

Weighting is carried out by dividing the resting and working values for each metabolite by the grand mean of all the values listed in our data file for that metabolite--about 2,000 values.

Eq. (1)

$$\frac{X}{\bar{X}_G} = X_W \; ; \qquad \frac{Y}{\bar{Y}_G} = Y_W$$

X = baseline value (nocturnal sleep specimen) for given metabolite (st, e, or ne)

Y = working value (pooled 8-hour-shift specimen) for given metabolite (st, e, or ne)

$\overline{X_G}$ = grand mean of all values for given metabolite (st, e, or ne)

X_W = weighted baseline value for given metabolite (st, e, or ne)

Y_W = weighted working value for given metabolite (st, e, or ne)

An individual index is calculated for each of the three urinary constituents.

Eq. (2)

For 17-ketogenic steroids: $(X_{Wst})\ (Y_{Wst}) = c_{st}$

For epinephrine: $(X_{We})\ (Y_{We}) = c_e$

For norepinephrine: $(X_{Wne})\ (Y_{Wne}) = c_{ne}$

c_{st} = individual stress index for st; c_e = individual stress index for e; c_{ne} = individual stress index for ne

The final composite index is calculated from the average of the three individual indices.

Eq. (3)

$$\frac{c_{st} + c_e + c_{ne}}{3} = C_s$$

C_s = composite stress index

The average of the three individual indices is used so that other measurements can be included if desired. Since C_s is dimensionless, any measurement can be used for which there are baseline and working values and for which a grand mean can be calculated.

This index is essentially a product of normalized baseline and working values rather than a ratio of the baseline value to an incremental change under working conditions. The product is used to avoid certain inconsistencies inherent in the ratio index, which is essentially a percentage expression. If a high level of stress under baseline conditions increased very little, or not at all, under working conditions, a stress index calculated from the increment-to-baseline ratio would be small. On the other hand, if the baseline value was very low and the increment only moderate, the ratio stress index might be quite large. This situation would lead to an erroneous interpretation of the level of stress. These difficulties are avoided with the product index in which the baseline and working values are integrated. C_s can be calculated for individuals, shifts, facilities, or any condition, provided both baseline and working values of the three metabolites can be obtained.

Comparison of air traffic control (ATC) facilities has been facilitated by the use of C_s (Table 1). Eleven studies were carried out at eight ATC facilities. These studies were designed to relate physiological stress to operational variables, such as workload, shift rotation pattern, type of work, and the effects of automation.

The ATC facilities listed in Table 1 are ranked according to C_s. The individual indices (c_{st}, c_e, and c_{ne}) from which the values of C_s were calculated are also shown.

The data in Table 1 are illustrated on the Streng triangles in Figure 1.[4,5,6] In this figure the values of c_{st}, c_e, and c_{ne} are represented as vectors diverging at angles of 120° from a common point. Lines drawn perpendicular to the ends of the vectors form an equilateral triangle. The theorem upon which this figure is based states that the sum of the perpendicular distances of any interior point from the sides of an equilateral triangle is equal to the altitude of the triangle. The altitude of each triangle is equal to the sum of the individual vectors; therefore, the area of the triangle is directly proportional to C_s (total stress), which is the average of the three individual vectors. The triangles can simply be ranked according to size for a quick overview of comparative amounts of stress at ATC facilities.

Qualitative appreciation of stress at the various ATC facilities can be gained from examination of the vectors inside the triangles. For example, it is apparent from Figure 1 that norepinephrine was the principal contributor to total stress at Opa Locka Tower (OPF), Atlanta Center (ATL), and Miami Center (MIA), and at Los Angeles TRACON (LAX) in 1972 (prior to installation of automated air traffic control equipment). Epinephrine was the principal contributor to total stress at Oakland TRACON (OAK) in 1972 (prior to automation) and Fort Worth Center (FTW). Steroids were the prime determinant of stress at O'Hare Tower (ORD)[7] and Houston Intercontinental Tower (IAH) in 1970.[8]

The disproportionate excretion of these three substances can be related to certain conditions that were known to be present at the various facilities. At Opa Locka, the 10th busiest airport in the United States, workload was estimated from the total time that each controller spent in radio contact with pilots. Table 2 shows that this measure of workload was not significantly correlated with c_{st}, was correlated with C_s and c_{ne} at the 5-percent level of significance, and was correlated with c_e at the 1-percent level of significance. Thus, it appears that c_e is the best single workload index of the three metabolites, with c_{ne} being a strong second.[3]

At the time of the study at O'Hare Tower in 1968,[7] a high level of stress was apparent even to a casual observer. O'Hare was then, and is today, the busiest airport in the world--about 2,000 aircraft operations per day. In the summer of 1968, O'Hare Tower was staffed at about 45 percent of its authorized level; most controllers were working 6-day weeks. A massive service slowdown by air traffic controllers elsewhere in the nation was in effect as a part of their efforts to effect changes in the ATC system and to gain increased benefits for themselves. The slowdown resulted in departure delays of several hours for airliners at O'Hare, creating massive congestion on the ramps and taxiways. Other contributing factors were a high level of labor-management tension, antiquated equipment, and uncomfortable and inconvenient physical facilities. These stressors, taken together, caused all three of the individual indices at O'Hare to be relatively high, with c_{st} being disproportionately high (ORD, Figure 1). The comparatively high values of c_e and c_{ne} are interpreted as being due to the intensity of the work arising from the dense air traffic at O'Hare. The high value of c_{st} is interpreted as being reflective of the chronic stressors related to labor-management problems, dissatisfactions with the work conditions, and fatigue resulting from overtime work.

Conditions at Houston Intercontinental Tower in 1970 were, in some respects, similar to those at O'Hare Tower in 1968. At the time of our study in 1970,[8] the IAH controllers had just concluded a "sick out"--an illegal strike. There was a great deal of labor-management tension resulting from the strike. The new Tower Chief had instituted a shift rotation schedule that the controllers did not like. The traffic at IAH was moderate--about 500 aircraft operations per day--and the physical facilities were excellent, consisting of a new tower and a new airport. The Streng triangle (Figure 1) shows a disproportionately long c_{st} vector and short c_e vector, interpreted as reflecting the chronic stress of the labor-management tension and the moderate workload respectively.

In 1971, tensions at IAH had eased considerably and the controllers had returned to the shift rotation pattern that they preferred--one that allowed a break of 80 hours between workweeks.[9] The Streng triangle shows a slightly diminished total stress and a somewhat more symmetrical internal arrangement of the vectors, particularly a shortened c_{st} line. This example shows how the diagram can be used by management as an aid in the evaluation of personnel and procedural adjustments.

Opa Locka Tower is an extremely busy facility at a high-density general aviation airport. The effort required to work the extremely dense general aviation traffic (about 1,000 operations per 16-hour day) is reflected in the relatively large values of c_e and c_{ne}, which are significantly related to workload (Table 2). Opa Locka Tower, however, did not have the chronic problems that were so apparent at O'Hare. Morale was good at Opa Locka and off-duty life appeared to be satisfying. The relatively low value for c_{st} appears to corroborate these observations.

Automated Radar Terminal Service (ARTS-III) is a computer-based, cathode-ray-tube display of aircraft identification providing range, azimuth, altitude, aircraft number, and speed. ARTS-III, by providing positive aircraft identification and altitude, contributes enormously to safety in crowded terminal airspace.

Studies to assess the effects of ARTS-III on controller stress were carried out at Los Angeles and Oakland TRACONs (Terminal Radar Approach Control).[10] The first studies were made in 1972 prior to the installation of ARTS-III, and the second studies were made in 1974 after ARTS-III was operational. The same subjects participated in both studies. The results (Table 3) show a marked decrease in steroid excretion by the groups in 1974. The increase in catecholamine excretion was so great, however, that total stress at these facilities was markedly increased. These data are interpreted to mean that ARTS-III, by providing positive assurance of aircraft separation, allays controllers' fears about mid-air collisions. However, the effort required to control traffic with ARTS-III was not reduced and may, in fact, have been increased. The increased excretion of catecholamines by these working controllers would seem to confirm their statements that the effort is greater with than without ARTS-III. The Streng triangles in Figure 2 graphically present the stress indices calculated from the data in Table 3 and shown in Table 1. The increase in total stress is obviously accounted for by the increases in catecholamine excretion. These catecholamine increments are probably due to the greater effort that controllers claimed was required to work a traffic load that had increased by about 10 percent from 1972 to 1974. Thus, one would conclude that total stress increased in the post-ARTS-III condition and that the increase was entirely due to acute stress brought on by an increase in the effective workload.

As was mentioned earlier, C_s is dimensionless and any other measurement can be incorporated into it, provided 1) a grand mean can be computed for the measurement, 2) resting and working values can be obtained, and 3) statistical requirements regarding such things as numbers and times of observations can be met.

In most studies reported here, except for those at the Atlanta and Fort Worth Centers, heart rates were recorded throughout the controllers' work periods. Pre-work (resting) heart rate values were also determined, though not for the same length of time as that for the working heart rates. An individual index for heart rate, c_h, was calculated and incorporated into C_s. Table 4 shows the comparison of C_s for the various facilities with and without inclusion of c_h. Correlation of c_h with C_s, c_{st}, c_e, and c_{ne} is shown in Table 5. It is clear that c_h is strongly correlated ($P \leq 0.001$) with c_e and c_{ne}; c_h is consequently also strongly correlated with C_s. Under circumstances when only heart rate can be recorded, strong inference can be drawn regarding catecholamine excretion, though nothing can be inferred regarding which catecholamine is being principally liberated.

In summary, it can be said that complex biochemical and physiological data can be normalized by simple methods and a composite stress index can be computed from these values. This index, C_s, is the average of the contributing biochemical and physiological measurements. C_s and the contributions of the three principal biochemical stress indicators (st, e, and ne) can be represented diagrammatically as vectors contained within an equilateral triangle, the area of which is proportional to C_s. These triangles allow quick comparisons between groups, individuals, work conditions, or other variables. Such comparisons are useful in presenting these complex biomedical data to layman managers whose needs and interests are pragmatic rather than scientific.

TABLE 1. C_s, c_{st}, c_e, and c_{ne} for Each ATC Facility Studied (Ranked by C_s)

Facility	C_s	c_{st}	c_e	c_{ne}
Fort Worth ARTCC	0.34	0.22	0.58	0.20
Los Angeles TRACON (1972)	0.60	0.66	0.34	0.81
Oakland TRACON (1972)	0.60	0.62	0.76	0.43
Houston Intercontinental Tower (1971)	0.68	0.89	0.62	0.52
Oakland TRACON (1974)	0.72	0.23	1.31	0.61
Houston Intercontinental Tower (1970)	0.74	1.27	0.29	0.65
Miami ARTCC	0.76	0.61	0.71	0.96
Los Angeles TRACON (1974)	0.78	0.30	0.94	1.09
Atlanta ARTCC	0.82	0.76	0.34	1.37
Opa Locka Tower	0.84	0.64	0.74	1.15
O'Hare Tower	1.05	1.41	0.75	0.98

TABLE 2. Correlation Coefficients of C_s, c_{st}, c_e, and c_{ne} and Workload

	Workload (transmission time)	P
C_s	.64	≤ 0.05
c_{st}	.19	N.S.
c_e	.77	≤ 0.01
c_{ne}	.55	≤ 0.05

TABLE 3. Comparison of Levels of Urinary Stress Metabolites at Los Angeles and Oakland TRACONs Before and After ARTS-III Installation

	st			e			ne		
Facility	Rest	Work	Δ	Rest	Work	Δ	Rest	Work	Δ
Los Angeles TRACON (1972)	521	1153	631*	0.4	1.2	0.8*	2.1	4.3	2.2*
Los Angeles TRACON (1974)	383	700	317*	0.8	2.0	1.2*	3.3	5.4	2.1*
Δ	138**	453*		0.4***	0.8*		1.2***	1.1***	
Oakland TRACON (1972)	485	899	414*	0.4	1.3	0.9*	1.6	2.6	1.0*
Oakland TRACON (1974)	319	679	360*	0.8	2.3	1.5*	2.2	3.5	1.2*
Δ	166*	220*		0.4*	1.0*		0.6**	0.9*	

* $P \leq 0.01$
** $P \leq 0.05$
*** N.S.

TABLE 4. Comparison of C_s With and Without c_h

Facility	C_s Without c_h	C_s With c_h
O'Hare Tower (1968)	1.05	1.07
Opa Locka Tower (1972	0.84	0.84
*Atlanta Center (1973)	0.82	
Los Angeles TRACON (1974)	0.78	0.88
Miami Center (1972)	0.76	0.84
Houston Intercontinental Tower (1970)	0.74	0.80
Oakland TRACON (1974)	0.72	0.80
Houston Intercontinental Tower (1971)	0.68	0.75
Oakland TRACON (1972)	0.60	0.72
Los Angeles TRACON (1972)	0.60	0.69
*Fort Worth Center (1973)	0.34	

*Heart rates not recorded

TABLE 5. Correlation of c_h With C_s, c_{st}, c_e, and c_{ne}

Index	c_h	P
C_s	0.56	≤ 0.001
c_{st}	0.16	≤ 0.05
c_e	0.28	≤ 0.001
c_{ne}	0.39	≤ 0.001

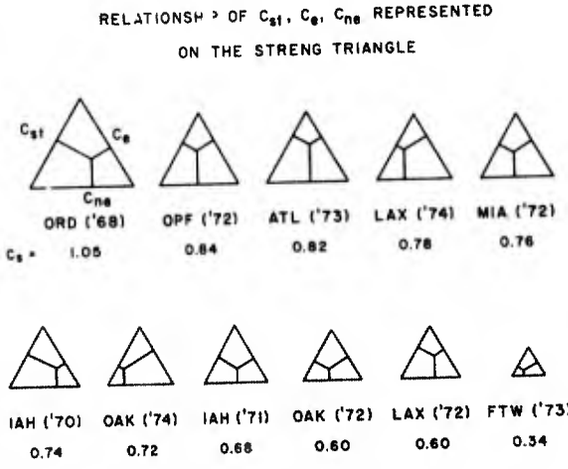

Figure 1

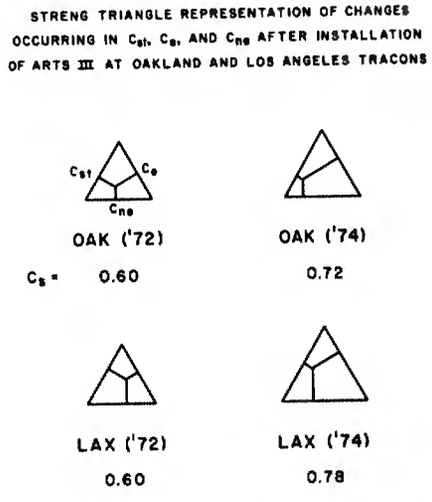

Figure 2

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THE FIELD ARTILLERY FIRE DIRECTION CENTER AS A LABORATORY AND FIELD STRESS-PERFORMANCE MODEL: I. POSITION PAPER; II. PROGRESS TOWARDS AN EXPERIMENTAL MODEL

LTC J.W. Stokes, MC, L.E. Banderet, Ph.D., R.P. Francesconi, Ph.D.,
A. Cymerman, Ph.D and J. B. Sampson, Ph.D.
US Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760 USA

SUMMARY

The 5-man fire direction center (FDC), common to all Field Artillery batteries, was chosen for study in the laboratory and field to evaluate the impact of environmental and situational stress on the complex performance of highly trained and motivated individuals working together as a team. The working environment of a field FDC was simulated within a hypobaric chamber and a volunteer FDC team from an elite U.S. Army unit was tested using realistic matched "combat" scenarios. To minimize practice effects, the team was initially given 26 h of "intensified training" (ITS). The team was then tested single-blinded as to the altitude condition for 48 hours at both 427 m (control) and 4242 m; the team rested 22 h between ITS and control and 48 h between control and the high altitude conditions. Mission performance during ITS and control was sensitive to disrupted sleep-rest cycles, with errors clustering at times of low arousal. At high altitude, performance was less efficient during the first 10 h; most serious errors involved processing of digits. Overlearned FDC skills showed little deterioration even when the men were ill with acute mountain sickness; compensatory behaviors were evident and technical performance for the last 38 h at altitude equalled or exceeded control. Thus, in this study communications, psychomotor, and judgment aspects of FDC performance, as well as measures of symptoms, mood, and neuroendocrine response, appear differentially sensitive to psychological stress, hypoxia, and fatigue. The rationale and objectives of this program are given (Part I) as well as initial experimental results (Part II).

ABBREVIATIONS

AMP = adenosine monophosphate
AMS = acute mountain sickness
EKG = electrocardiogram
FA = Field Artillery
FDC = fire direction center
FDO = fire direction officer
FO = forward observer
FSO = fire support officer
GFT = graphic firing table
h = hours
HCO = horizontal control operator
ITS = intensive training session
RTO = radio telephone operator
USARIEM = U.S. Army Research Institute of Environmental Medicine
VCO = vertical control operator

I. POSITION PAPER

The ability of Army communications and command/control personnel to carry out their duties quickly and accurately under pressure is often crucial to their unit's successful performance of mission. A number of factors suggest that it may be among these critical personnel that tactically significant decrements occur during sustained operation without relief (1,2) following rapid translocation across time zones (3), and/or in physical environments drastically different from those to which they are acclimatized (4-6). The critical nature of their duties makes them less able to take time off to rest, and may require their round-the-clock alertness even during the deployment, staging, and redeployment phases. Research suggests cognitive performance rather than more active and "automatic" perceptual motor tasks is disrupted by sleep loss, fatigue, and subtle disturbances of brain biochemistry and physiology (7). While the arousal produced by danger, physical exertion, or novel stimuli protects even mental tasks against decrements due to fatigue, these personnel are more likely than others to be unaware of immediate personal danger, to be isolated from immediate feedback as to the correctness of their performance, and to work in confined areas for long periods where body movement and sensory and social stimulation are limited. Their motivation must therefore be sustained by the knowledge that an inaccurate communication or even an unnecessary delay in transmission is likely to have disastrous consequences extending far beyond their own immediate unit. It is this last fact which makes communication and command/control personnel especially deserving of research to determine their realistic human limitations under adverse conditions and to develop ways of utilizing or augmenting them to extend those limits.

Scientific analysis of communications and command/control performance in real-life settings has always been difficult. The cognitive processes underlying decision-making are difficult if not impossible to quantify and measure. The relative superiority of alternative courses of action is hard to gauge when only one alternative is carried out, and comparisons in the field of different units performing similar functions or comparisons of the same unit performing in differing situations must be imprecise. Efficient teamwork may suffer even before the deterioration of any one individual's performance can be demonstrated. And, finally, many failures in judgment or communication are errors of omission which can only be inferred retrospectively when real circumstances conspire to reveal the lapse. For these reasons, the field investigator must often reach conclusions on the basis of global ratings about "satisfactory" vs "unsatisfactory" mission accomplishment and general "clinical impressions" of efficiency.

Efforts to study such complex functions in the laboratory with tests of task components or factors, however, face even more serious objections. Components isolated from real world tasks can be combined to form a synthetic representation (8,9), but unless the synthetic representation is kept unrealistically simple, too much time will be spent training naive test subjects to some arbitrary criterion of proficiency which falls far short of overlearning sought by military training programs. An alternative is to bring actual military teams to the laboratory and test their efficiency while they perform their mission under carefully controlled conditions (10,11). If their interest, competitiveness and fear of failure can be invoked, this will presumably mobilize the reserves of concentration and arousal which make performance

in the clearly defined crises of combat remarkably resistant to decrement. In order to study such a naturally occurring model Army command/control and communications team, the model must be suitable for measurement with naturalistic observational techniques which do not interfere with the work of any individual or the group. The model tasks should also have intrinsic records which can by analyzed, allow embedding of measures, and have recognized and accepted criteria (standards) of acceptable operational performance. To insure that the model is sensitive to even moderate levels of stress, performances studied should range from highly overlearned, repetitive actions to more complex abilities involving evaluation of information and decision-making. Some tasks should be force-paced (prompted by the demands of the situation) and others self-paced (initiated by an individual).

In studying a real team while they perform their mission under carefully controlled conditions, two categories of behavior can be measured to provide correlation with each other, with physiological and biochemical measures, and with global measures of mission performance. The first, which enjoys high face validity, consists of components of communication or command/control tasks which can be defined operationally and scored in terms of accuracy, speed of performance, and completeness. Some tasks should involve extreme time pressure while others should be self-paced. Frequency of occurrence should approximate field occurrence, but the frequency must be sufficiently high to permit statistical analysis of the parameters measured. In a planned study, whether it is a field experiment or a laboratory simulation of field conditions, events should be scheduled as part of an overall scenario to insure that information load, mission demands, and specific types of missions are matched in time and across conditions.

The second class of measures would be behaviors which are not directly involved in the performance of mission, i.e. non-task behaviors such as smoking, eating, laughing, joking, and complaining, whose spontaneous frequency or qualitative expression over time may reflect changes in mood, alertness, motivation, or other physiological and biochemical factors. These indices may prove valuable in estimating the likelihood of covert errors or the performance potential still in reserve.

We concluded from anecdotal accounts, field observations, and a literature search that the Field Artillery (FA) fire direction center (FDC) is a suitable Army command/control and communications team for study (12,13). The FDC is ubiquitous and critical to most Army tactical operations and is exposed to and reportedly shows effects of environment, mental stress and fatigue. This team task is ideally suited for study in the laboratory as it can be realistically simulated in an environmental chamber. Input to the FDC as well as the response to output from the FDC can be controlled and played realistically. Because the essential team is confined to a small space, simultaneous non-invasive observation (or collection of video and audio records), fractional urine collection, and telemetered biomedical monitoring are possible.

In the development of this program, we will test teams with standardized, "realistic" scenarios in the laboratory. There we can control environmental variables and be fairly certain that we can induce noticeable changes in FDC performance with time. Video and audio records, collected during laboratory experiments, of normal performance as well as performance after it has deteriorated, will enable us to replay and analyze these events so that we can identify stress-sensitive task indices of FDC performance and determine the relationship of these performance changes to other classes of measures. We also expect to identify subtle shifts and changes in emotional, social, and self-paced behaviors which may be predictive of later changes in team task performance. After we have identified and quantified our indices of task and non-task behaviors, we will be in a position to test the effects of less stressful environmental conditions on the FDC and to test the validity of our model during medically-devoted field experiments. If our model is valid, then we anticipate that our findings can be generalized to other military teams with less clearly quantifiable missions, such as company command posts, tactical operations centers at battalion, brigade and division levels, and other staff and logistical teams, as they function in field operations.

We will describe some of the procedures and command/control functions which occur in the FDC to give an appreciation for the complexity of these tasks and the conditions under which the tasks are performed. It is our opinion that great potential exists for the study of judgment, decision-making, integration of information, and the use of unobtrusive and embedded measures in the study of this Army team task. We think you will see some of the reasons why the study of FDC performance is an expedient and useful model for the assessment of human performance under stress.

Fire direction centers operating in the field are housed in a variety of small, confined shelters. Depending upon the unit, this may be an M577 tracked command post vehicle, the back of a gamma goat with a test extension, a closed area built onto a truck, or two conex metal containers set end to end. Contact and information from other units operating in the field comes into the FDC primarily by radio and telephone and by occasional printed communications. The men normally do not leave the FDC unless briefly during lulls to get food or relieve themselves; they sleep when they can, next to their stations. To quote the introductory course written by the Field Artillery School, Ft. Sill, "The FDC in any unit must be organized for 24-hour operation. Round-the-clock operation requires that the FDC personnel know each job and that replacement personnel be trained within the unit. Improvement of performance in the FDC will continue as long as the position is occupied. All personnel in the FDC must understand that the reason for their being in the FDC is to prepare data for the delivery of fire as quickly and as accurately as possible."

The battery FDC, as well as higher-level FDCs, is an interacting system in which system output is dependent on each member's functioning and interaction with other members of the team. The typical battery FDC is composed of five men; each member of the system has well-defined roles, duties and responsibilities. During a fire mission, the FDC's standing operating procedures specify who talks to whom, what is said, and the sequence for these communications. Independent determinations of most data and checks on all information calculated and communicated in the FDC makes this a highly evolved system with error detecting and self-correcting capabilities. During normal FDC operations several intrinsic records are generated by the FDC that can be later scored for their accuracy and completeness. Such records include the radio-telephone log, computer forms, situation overlays, and acetate plotting sheets of the control operators. The fire direction officer (FDO), a Lieutenant, is the highest ranking member of the battery FDC; he is responsible for coordination and supervision of the FDC and ultimately for its success or failure. During

a fire mission the FDO inspects the plot of the reported target, decides how to attack the target, issues the preliminary fire order to the battery, and checks the accuracy of computations and information generated by the other members of the FDC team.

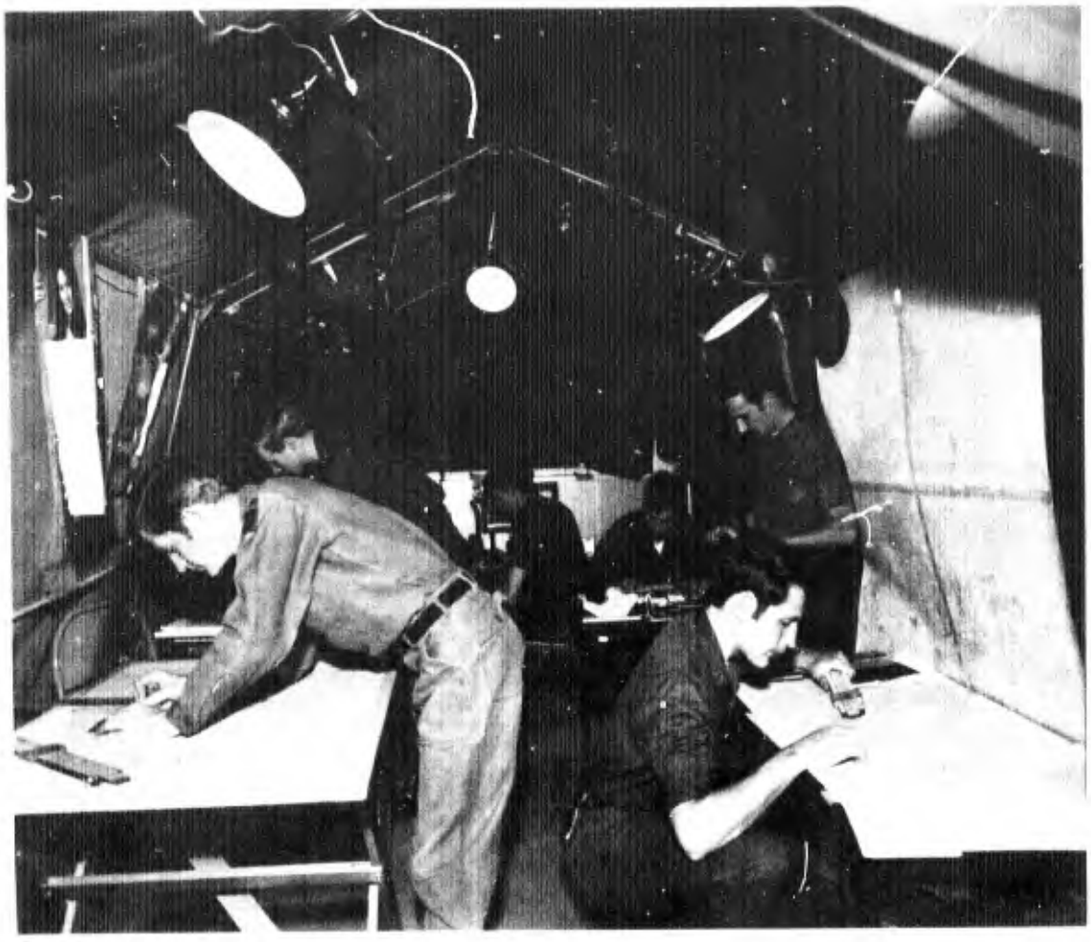

ILLUSTRATION 1 - A battery FDC erected inside a hypobaric chamber for the laboratory study of individual and team FDC performance during exposure to environmental stress. Normal FDC operations utilize a 5-man team, but in this situation an additional man has been added as a backup. On the left the HCO and VCO are at their control charts, and the RTO is seated by the radios in the rear of the FDC. The computer is seated at the table calculating firing data as the FDO is crouched examining the situational overlay to insure that the target can be engaged. The extra man is assisting the team by calculating an elevation correction (site).

Incoming calls for fire from a forward observer, aerial observer, higher headquarters, or a unit being supported by the Field Artillery are received in the FDC by the radio-telephone operator (RTO). He is usually the lowest ranking member of the team; he makes periodic communications checks on the radio and telephone nets and receives all incoming requests for fire. As each call is received, he maintains a log and repeats back elements of the call for fire to insure that he and the other members of the team heard the message correctly.

The location of the target is plotted on a 1:25,000 scale grid sheet by the horizontal control operator (HCO), who determines the target's range and deflection with the metal protractor and immediately calls these numbers aloud to the computer. The vertical control operator (VCO) also plots each target and provides an independent check on the HCO. The VCO also determines if the altitudes of the firing battery and the target are different by consulting a terrain map of the area. Using a slide-rule-like device he computes an elevation correction based on the difference between the target and gun altitudes and the target range. The VCO relays this value to the computer when it is requested. The VCO also maintains an overlay on his vertical control chart which shows the changing tactical situation, "no-fire zones" and areas where artillery fires must be restricted. When the FDO determines how to attack a target, the VCO may assist the FDO in the choice of ammunition charge and lot.

The computer, an E-4 or E-5, is the highest ranking enlisted man in the FDC. His task demands, responsibilities, and training are greater and more demanding than those of the HCO, VCO, and the RTO. When an incoming call for fire is received, the computer records the call for fire and the FDO's initial fire command on a standard FA form. He then telephones the initial fire commands to the battery, adding

any standard elements which the FDO may have omitted. Next, the computer repeats aloud and records the range and deflection announced by the HCO, manipulates the appropriate graphical firing table (GFT), another large slide-rule-like device, and reads off the corrected deflection to the battery. Finally, he repeats aloud the elevation correction supplied by the VCO, adds it to the elevation given on the GFT and telephones this information to the battery. Only a few seconds more are required for the gunners to finish setting their gunsights, align the barrel, load, and fire. The time interval between the FO's call of "Fire Mission!" and this last instruction to the firing battery is obviously of great tactical importance in combat and a well-trained unit can complete all the procedures in approximately 60 sec.

The activities and the sequences of behavior just described deal primarily with force-paced activities which are an inherent part of normal FDC operations. The FDC also has many self-paced activities which should be completed during lulls in activity; these activities are important since they can greatly influence the accuracy and the timeliness of subsequent artillery fires. Self-paced activities in the FDC include updating ballistic corrections with the most recent meteorological data, replotting of targets relocated by survey or precision registrations, keeping informed of the current tactical situation plotting potential targets of opportunity acquired from intelligence sources, updating "no-fire zones", cleaning and improving the appearance of the horizontal and vertical control charts, working up data for preplanned fires, and updating records, etc. We view this class of behaviors with great interest since the self-paced activities are intended to be done during a period when the mission demands no longer determine FDC team behavior. That is, these self-paced activities present situations where the FDC team members can choose what they wish to do; the choice of alternatives and the intensity and duration of behaviors during lull intervals will likely provide some of our most sensitive indices of stress.

Initially, we are studying airborne manual FDC teams since such units must maintain a manual fire direction capability and they are also the units most likely to deploy rapidly to a harsh environment. It should be understood that we do not anticipate that the FDC team is more prone to performance decrements under stress than other command/control and communication teams (14). On the contrary, because its procedures have been so thoroughly structured and over-learned, it is probably less likely to fail than other teams with less clearly defined roles. Since the FDC's margin for error is so small, its efficiency can be measured precisely, and its system for internal error correction is open to objective measurement, small changes observed in FDC performance may warn of potentially disastrous changes which might occur in other systems.

In conclusion, we feel that the study of an actual Army team can provide a model from which useful operational and scientific data can be derived. We are excited by this approach since we feel it represents a meaningful way to determine the effects of extreme environments upon a critical military team task. After the model has been developed, we shall use the stress-performance model to evaluate the efficacy of acclimatization and other therapeutic regimes used for the prevention or treatment of environmentally-induced disorders. We feel that the FDC is also an appropriate model to evaluate other stressors. Since FDC operations can be simulated in the laboratory or in the field with a minimum of personnel or equipment, this approach would be an expedient way of studying the effects of rapid deployment across several time zones, extended operations, fatigue, lack of sleep, etc. on performance. We think that in studying the FDC, which involves an actual military team, we will be aided in the development and use of valid and meaningful measures of military performance which may ultimately be translated into operational guidelines for stressful conditions.

II. PROGRESS TOWARDS AN EXPERIMENTAL MODEL

This paper reports performance data from our second (pilot) study of the FDC. Simulated high altitude (4242 m) was chosen as the environmental stressor since we felt that its more predictable effects would facilitate identification and quantification of stress-sensitive indices. Other dependent variables are also reported to illustrate our multidisciplinary and multivariate approach. We will describe why we feel that the FDC has potential as a model for the study of higher mental functioning and a wide range of other performances.

METHODS

Ss

Test personnel were 6 volunteers (extra man for backup) from a 105 mm howitzer battery of an elite Army Airborne Unit.

Apparatus

A representative FDC facility was created with an Army 5-man tent erected within the USARIEM hypobaric chamber and furnished with authorized FDC Army equipment. The equipment included maps, control charts and plotting equipment, graphical site tables, and tabular and graphical firing tables. In a separate chamber a "command post" was established for 8 additional Artillery personnel from the same unit who played the roles of FO, FSO, etc. as specified in the scenario scripts. Communications between these personnel and the FDC was with Army field radios and telephones. Video (with time-date generator markings) and audio recordings of activities in the FDC were collected continuously during each test condition from video cameras and omnidirectional microphones positioned unobtrusively within the FDC. A continuous EKG recording was determined for each individual in the FDC by radio-telemetry.

PROCEDURE

During the simulation, 14 artillery personnel were utilized. Of these, 6 people (an actual battery FDC team supplemented with a computer from battalion) were tested. The remaining 8 artillery personnel were in the "command post". They called in information to the FDC and responded to the output from the FDC as they "played" the roles specified by the scenario scripts. Their actions were supervised by USARIEM scientific personnel to insure that events in the scenario were played as specified. The script players were in a chamber at the opposite end of the Institute and communications between the FDC and them were by

Army field radio or telephone. On occasion, the FSO went into the FDC to brief personnel (timing and content specified by the scenario) or to deliver Operation Orders. During the entire duration of the study the only contact that occurred between the FDC and the script-player teams was that specified by the scenario. We carefully selected the personnel required as role players for this simulation from the artillery unit. By doing so we were able to greatly increase simulation realism as well as the involvement of the team being evaluated. For example, the Officer in Charge of the script players was actually the battalion gunnery evaluator (scorer) from the parent unit of the tested battery.

a. Environmental Conditions

The team was tested in the FDC under simulated operational conditions on 3 separate occasions. Initially, they participated in an "Intensified Training Session" (ITS) for 26 h at low altitude (427 m) to minimize practice effects, followed by a 22 h rest and relaxation period in the Institute barracks. They were then tested for 48 h at 427 m (low altitude control), rested 48 h, and evaluated for 48 h at 4242 m (high altitude) followed immediately by a gradual descent from 4242 to 427 m with operations continuing for 5 h at low altitude. In the 2 days prior to the ITS, baseline biochemical, symptom, and mood parameters were determined and the men were oriented to the Institute and briefed on the hypobaric chamber facility. All altitude conditions were single blinded; in the initial briefings the FDC team was told "the chamber altitude during a simulation interval might be anywhere from 427 to 4242 m and that operations after the ITS would last anywhere from 30 to 60 h." The FDC was advised to set up work shifts so that each member of the team would get some sleep. The ambient temperature inside the FDC was maintained at 68 $\pm$ 2°F with 30 $\pm$ 5% relative humidity.

b. Scenario Scripts

The scripts specified with time the sequence of events, the flow of information, mission demands, work-rest cycles, as well as the duration and frequency of intervals when there were lulls in the mission demands. The basic principle was to match events in each scenario as closely as possible so that for almost every fire mission in the low altitude scenario there was a fire mission at the same time in the matched high altitude scenario using a different terrain map which involved the same number, types and sequence of computations, similar urgency and emotional impact, and similar demands for judgment. This was also true for the few instances in which the scenarios were written to produce an "overload situation" by having the FDC respond to simultaneous requests for fire support from multiple forward observers. To facilitate statistical comparisons within the same scenario over time similar kinds of missions occurred at approximately the same time each day, and the more routine kinds of missions occurred 4 to 6 times each 24 h. To prevent the temporal pattern from becoming obvious, occasionally a unique or idiosyncratic mission was included, but even these had a subjectively equivalent mission at the same time in the other scenario. Information load in the form of FO reports and preplanned target lists were also matched over time, although not on an event-for-event basis.

Obviously, the content of the scenario script, e.g. the specific calls for fire missions, meteorological messages, FO situation reports, determines with mathematical precision the correct answers for each step in the computation of firing data. But the scenario must be more than just a succession of fire missions coming in a prescribed sequence if it is to evoke the real-world life and death associations and motivations of the participants. To test decision making and judgment (including recognition of when information is erroneous and should not be acted on automatically), each scenario must be a coherent "command post exercise", simulating what the FDC would receive during a real military operation across the terrain represented by the maps. This "tactical realism" made the experiment attractive adventure training for the FDC team, but of greater importance it increases the probability that the performance, physiological, biochemical and behavioral data will be valid.

The scenario scripts provided structure for activities in the FDC during the simulations. Fluctuating workload and increasing fatigue with sleep deprivation were matched across the control and experimental conditions. Also matched were opportunities for fraternization with the artillery personnel role playing the scenario scripts as well as the scientific data collectors, identified by the scenario as medical service corps personnel on special duty in the combat theater, who periodically entered the FDC to administer symptom questionnaires, mood scales, etc. Lulls in the action were also regulated so that there were opportunities for self-paced mission performance, social interaction, and individual and group non-task behaviors; the spartan furnishings of a field FDC tended naturally to standardize leisure activities.

c. Symptom Reports, Mood States, Urines and Blood Samples

Self-rated symptom reports from the General High Altitude Questionnaire (15) and mood states from the Clyde Mood Scale (16) as well as total urine outputs were collected every 8 h for the entire time that the team was available for study. During the chamber simulation, a member of the scientific team dressed in Army fatigues entered into the FDC for less than 30 minutes each 8 h to administer the questionnaires and collect the urine samples. Urine samples were analyzed for cortisol, 17-hydroxycorticosteroids, cyclic AMP, and total catecholamines. Each day at 0730 h plasma samples were drawn and analyzed for cortisol, cholesterol, uric acid, dopamine-B-hydroxylase, and cyclic AMP. Cigarettes, hot chocolate, and coffee were not restricted at any time from the FDC personnel.

d. Observational measures

Every 15 minutes during the simulation, 2 scientific observers scored each member of the FDC team for the occurrence of a number of objective and discrete behaviors. These observers viewed video monitors which displayed activities inside the FDC and listened for verbal communications (task and non-task) within the FDC on headphones. Each behavior scored, e.g. working, sleeping, talking, and laughing, during an observational interval was based on a 12-sec. sample. The observers marked their data directly on perforated computer cards.

e. Electrocardiograms

Continuous EKG recordings were obtained from each member in the FDC. Electrodes were attached prior to a simulation and the EKG (2 lead) was transmitted from each individual by a miniature frequency-modulated telemeter. The EKGs were recorded on magnetic tape for subsequent analysis by computer.

RESULTS AND DISCUSSION

As expected from anecdotal field reports, firing data produced by the FDC proved susceptible to the effects of fatigue and altered sleep-rest cycles during the ITS and control scenarios at low altitude. These data are consistent with reported symptoms, mood states, and several biochemical indices which increased over nonoperational values during these same periods. In addition, normal diurnal variations in several of the biochemical measures were disrupted during these low altitude simulations.

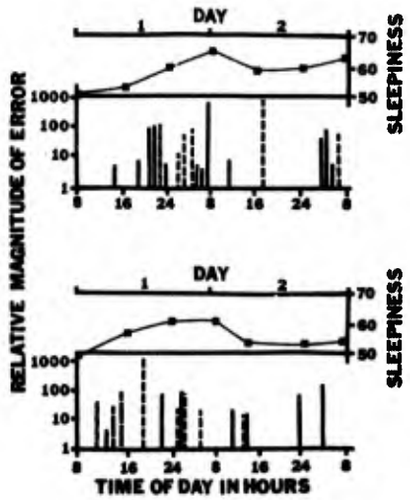

FIGURE 1. Various FDC performance errors with time during the simulated 427 m low altitude (upper graphs), and 4242 m high altitude (lower graphs) conditions. Information to the FDC, mission demands, types of fire missions, etc., were matched for the 2 conditions by prewritten "combat" scenario scripts. The relative magnitude of the error specifies approximately how far the rounds would have impacted from the target as a consequence of the error. Target location errors are shown as solid bars; use of a ballistic slide rule for a different charge than the one that was fired is shown as broken diagonal bars; data processing errors as long dashed bars; and list reading errors, as short dashed bars. Also shown are team averages for self-rated "sleepiness" on the Clyde Mood Scale; larger numbers indicate greater sleepiness.

Figure 1 shows the time course and relative magnitude of errors in the initial firing data; the relative magnitude of the error shows approximately how far each round would have fallen from the target. During the low altitude control scenario (upper graph), most errors occurred in the late evening and early morning between 2200 and 0700 h, and were usually due to lapses of attention and insufficient team integration during low priority missions. Some errors involved reading the wrong information from lists of anticipated targets of little tactical urgency for which the FDC had previously determined much of the necessary firing data during lulls in mission activities. Such errors are shown in Fig. 1 by the short dashed, broken bars.

The magnitude of these errors is largely a function of how the list was misread but the important datum is that a careless error occurred. Also significant is the breakdown in the FDC's internal system of double checks which did not detect these errors and allowed them to be sent "to the guns". Another common type of error (solid bar) resulted from the HCO plotting the target in the wrong area of the control chart so that an incorrect target range and deflection from the guns were determined. These errors usually resulted from substitution or transposition of digits in the grid coordinate. Whether a 10,000, 1,000, or 100 meter error resulted was dependent upon which digit was transposed. Such differences are of life and death importance in the real world, but viewed as scientific data, even the smaller errors are indicative of individual and team malfunction.

How does the time course of errors shown in Fig. 1 compare during low (upper graph) and high altitude (lower graph) conditions? The greatest contrasts at high altitude are the increased errors which occurred in the first 8 h and the lack of nocturnal errors on the second day between 2400 and 0800 h. Two of the

initial errors at high altitude involved number substitutions and transpositions within the firing data as it was processed and calculated by the FDC rather than errors which originated as the initial information was received from the FO's request for fire support. Unlike the low altitude nocturnal errors, these occurred in relatively high priority missions in which speed was important. These errors were committed by the hard-working computer, but were not detected by the FDO's doublecheck. The FDO also computed firing data using the wrong ballistic slide rule, i.e. a graphic table showing a different charge than the one he was shooting, in a high priority mission. This error was not detected by the computer, and the FDO did not realize the error himself until seconds after the volley began.

During the initial 8-10 h period at high altitude only one minor error was contributed by the horizontal chart operator. In the first few hours the regular HCO became so nauseated that he eventually was relieved by the extra man. Until that time, he sat slumped head down on his chart (after he had determined the chart data), even while missions were in progress, but there was no quantifiable change in his accuracy or the time he required to determine the target range and deflection compared with his performance at low altitude.

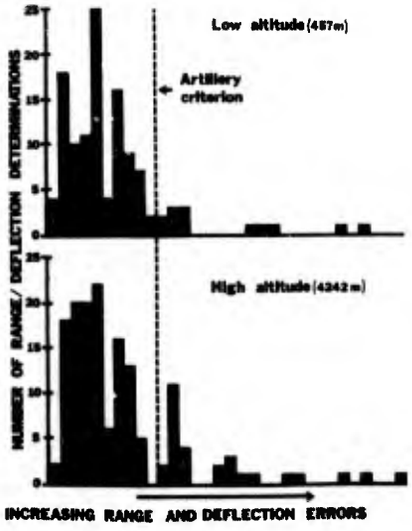

FIGURE 2. Horizontal control operator range and deflection accuracy during exposure to simulated low altitude (upper graph) and high altitude (lower graph). All range and deflection determinations to the left of the vertical broken line represent acceptable performance as specified by a Field Artillery criterion. The occurrence of several determinations to the immediate right of the Artillery criterion during the high altitude condition resulted because the HCO made a small error when the deflection indices were initially penciled onto the chart. This constant error then affected the accuracy of subsequent deflection determinations. Taken as a whole, these data indicate no significant differences in horizontal control operator performance during the low and high altitude conditions.

Figure 2 shows that there was no substantial deterioration in chart operator function during the 48 h high altitude exposure from that during control. Consistent with these findings, the manual and visual skills required of the computer and FDO in their use of the ballistic slide rules, together with the associated simple mental arithmetic, appeared minimally affected by altitude. Most errors that were observed involved the integration and transmission of information.

During the initial10 h at altitude when increased errors occurred, time taken to process the initial firing data for each mission was not greatly increased. After the initial data was fired, subsequent adjustments were sometimes requested by the FO to bring the rounds closer to the target. These adjustments are a simpler procedure for the FDC (and each team member) than determination of the initial firing data, but the time required to determine the firing data for such adjustments did show some diurnal increases at low altitude and increased during the first few hours at high altitude. By the 7th h at high altitude, on some missions, where speed was not essential such as harassment and interdiction missions, time for adjustments increased by as much as 100%, and such episodic changes were observed for the remainder of the high altitude condition. On those missions where increased time was required the FDO and computer were primarily responsible for the increases as the speed of the chart operators appeared minimally affected.

Such observations on performance are more meaningful when one is cognizant of other changes in the present study that were induced by altered sleep rest cycles, high altitude, and the discomfort of acute mountain sickness (AMS). Most members of the FDC team were mildly to moderately sick with AMS at high altitude. The team reported symptoms of reduced vitality and increased irritability, headache, and cardiorespiratory changes; some vomiting was observed. As is characteristic, most symptoms of AMS began about 8 h after ascent to altitude, were maximally severe 16-32 h after ascent, and decreased in severity with greater time at altitude.

Similar temporal changes in mood were documented. At high altitude, FDC personnel rated themselves as less friendly, more dizzy, and contrary to our expectations, less sleepy. These changes were most marked in the first 24 h with substantial improvements the second day at high altitude. Real-time observational measures indicated that during the first 24 h at high altitude FDC personnel sat, reclined, and huddled more than during the same period at low altitude. At altitude, huddling increased more than 200%, probably reflecting a response to the AMS symptomatology.

The results from many of the biochemical assays were not expected. Although daily urinary excretion of 17-hydroxycorticosteroids was greater at high altitude than during the ITS or the low altitude control, urinary cortisol and catecholamines as well as plasma levels of cholesterol, uric acid, cyclic AMP, and dopamine-B-hydroxylase were not elevated above ITS or low altitude control values. Plasma cortisol levels were greater during the ITS than during the subsequent low and high altitude conditions suggesting a "novelty" response to initial FDC operations in the laboratory simulation. Also unexpected was the fact that the FDO had one of the lowest plasma cortisol levels of any of the men under all conditions, even though he was responsible for the team's performance.

To date, the EKG records have not been analyzed in sufficient detail to determine if changes in cardiac parameters with time or with high altitude are predictive of changes in performance or other behaviors that were noted. It can be said that the expected tachycardia, i.e. increased heart rate, was observed as a response to high altitude.

It had been postulated that altitude and AMS might have a deleterious effect on the self-paced aspects of FDC performance such as preplotting of targets which might never be fired, but this was not observed. The team also committed fewer careless list-reading errors (short broken bars in lower graph of Fig. 1) especially during the second night at altitude, perhaps relating to the team's decreased sleepiness reported on the Clyde Mood Scale. As shown in Fig. 1 the circadian rhythm of errors and sleepiness, like the circadian rhythm of the biochemical parameters, was disrupted more by the high altitude than the earlier low altitude condition.

Thus far, the performance data that we have reported, has been primarily concerned with the basic skills involved in the processing of fire missions. While these required different levels of psychological complexity, most elements of the missions were routine and therefore highly overlearned by this professional team. Can the FDC model contribute any new perspectives to the topic of this meeting: the effects of operational environments on "higher mental functions", e.g. judgment and decision making in non-routine situations? Anecdotal accounts from military operations in very hot, cold, hypoxic and unremitting combat environments tell of inexplicable lapses, failures of perception, and altered mental states, e.g. unwarranted sense of well being, irrational and impulsive judgments, emotional outbursts, and flatness of emotion. How can such transitory, ephemeral and unprogrammable phenomenon be captured in the laboratory setting? How can such a unique phenomenon, once captured, be dissected and analyzed to determine its mechanisms? The following incident occurred in the FDC during this study and was recorded fully on audio and videotape. It is presented in detail to provide a concrete "case history" to illustrate how our approach with the FDC model lends itself to the assessment of higher mental functioning.

At 1815 h, the second day at simulated high altitude, the FDC received an "urgent contact" fire mission in which the FO included the standard warning which specifies that friendly troops are near the target. The computer's special instructions to the battery indicated that he, at least, perceived the potential danger in shooting this mission. Each of the next four adjustments of the artillery rounds from their initial point of impact moved the rounds closer to the friendly troops by the maximum increment specified in the Battery's Rules of Engagement. Then, the FO called for an adjustment in which the incremental shift was a definite violation of the rules; this adjustment, if fired, was likely to injure the friendly troops. The FDC processed the adjustment without comment! After the FDC fired this adjustment, the FO radioed in, "Checkfire! One of your rounds has landed among friendly troops!"

This was an error, but not an unprecedented one. The FDO's actions hours before indicated that he knew and was applying the Rules of Engagement and in similar situations at low altitude, the FDO had reacted decisively and with feeling, checking the control charts, maps, and firing data, and contacting the FO to resolve the problem. On this occasion, none of the men in the FDC reacted for several seconds, until the FDO prompted his men in a flat voice to merely relay the "checkfire" warning. The entire FDC team then waited passively, almost immobile, until the FO called in a new adjustment which was not in violation of the "Rules" and the mission proceeded. It is noteworthy that throughout the entire mission, all firing data produced by the FDC was prompt and accurate, and double check procedures were faithfully observed. However, the behavior of the team and the FDO in particular had an unusual automaton-like appearance. At the end of the mission, the FO reminded the FDC of the error and the FDO answered back with only a fraction of his usual animation, "Tell him we sent him what he asked for!" This "lapse" occurred in spite of the fact that the initial call for fire and each request for a subsequent adjustment by the FO gave the FDC sufficient information to recognize the danger. Subsequently, the team did show a better level of alertness in contact missions, and by the next morning (after 46 h at altitude) they had returned to "normal", i.e. the FDO adamantly refused to fire an adjustment which would endanger the lives of friendly troops. Furthermore, the FDO suggested a "legal" alternative for this adjustment even though the FO insisted that he knew what he was doing.

In a recorded debriefing following the study the FDO hardly remembered the incident of the checkfire and had to be given a step-by-step description of what happened. He insisted that, as best as he could remember, he had been taking his duties seriously at the time. He stated,

> "I didn't think I was going to be shooting up anybody even though it was a close mission. When they (FO's) start making bold corrections, you know, I try to remember to lift up the target grid (on the horizontal control chart) to see what I'm shooting at. I don't remember whether I did it then or not, but I wasn't concerned that we were shooting on top of someone because I didn't think there was somebody right there. And when he said we'd shot at somebody, I thought, well, maybe he's there and I didn't know about it."

COMMENTARY

Can such an observation of impaired individual and team "judgment" be shown to be related to high altitude hypoxia, the discomfort of AMS, fatigue, or to any other operational stressor? In the long run, we believe that the ultimate strength of the FDC model is that it creates a controlled and replicable setting in which lapses of judgment and imperceptive teamwork can be analyzed in depth from many viewpoints. Such incidents are recorded on video and audio tape and time markings allow specification of any visible or audible event to within one second. The error in judgment occurs in a specific context; the content of the scenarios develops a plausible and realistic series of situations which are written to promote just such lapses. The matched scenarios make it possible to compare the "lapse" with very similar situations in the matched control scenario. Systematic, "blind" observational measures of mood, morale, motivation, involvement in the scenario, and time since last rest or sleep are obtainable for each individual, along with his self-ratings, symptom reports, and the biochemical parameters for the epoch in which the lapse occurred (and for those epochs with similar situations in which it didn't). When the FDC model is fully operational, there will be EEG together with EKG records to document the cortical and autonomic state of the subjects during the interval the lapse was made and at the moment it was revealed. Finally, the fact that the real world consequences of such errors can be specified in terms of "where the rounds would have landed" highlights the importance, as well as the potentially disasterous effects, of such dysfunctions.

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DISCLAIMER STATEMENT

The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

This human research study, in protocol form, was reviewed and approved by the Office of The Surgeon General for the Department of the Army in accordance with Army Regulation 70-25.

EXPERIENCE WITH ELECTROENCEPHALOGRAPHY IN APPLICANTS FOR FLYING TRAINING 1971 AND 1972

by

H. OBERHOLZ, LtCol, GAF, MC
German Air Force Institute of Aviation Medicine
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Ever since the activation of the Bundeswehr (German Federal Armed Forces) electroencephalography has been an integral part of initial flying fitness examinations. Since 1973 the German Air Force Institute of Aviation Medicine routinely records EEG follow-ups in pilots and weapons system operators at ten year intervals.
There is agreement by authors reporting on the EEG in Aerospace Medicine that an EEG should be recorded from any aviation candidate prior to flying training. So far this requirement has not been met by all NATO air forces.
There can be no doubt that electroencephalography reveals indications for epilepsy. The French study group of BLANC et al. (5) deducted from long-term observations, that the EEG has an anticipatory value in finding psychic disorders. High expectations, however, that the EEG could serve as a precise indicator of cortical functions, have so far failed to materialize. There were many examinees, whose EEGs did in fact show considerable disturbances in repeated tracings, and yet no disease nor any performance decrement could be uncovered. Conversely, morphological alterations of the brain, which can be verified radiologically, will not necessarily show up in an EEG.

When using the EEG as a routine initial screening method in healthy adults, it is necessary that Institutes of Aviation Medicine develop and standardize criteria through international cooperation and coordination in order to achieve optimal results. Criteria must not be too strict and thus prevent healthy applicants from going into flying training. They should not be lenient either, allowing candidates with a latent central nervous system disease to go into flying training with a high rick of elimination later on.

The US Bureau of Medicine and Surgery promulgated criteria for defining abnormal tracings upon the recommendation of a conference in electroencephalography held at Pensacola in 1961. These criteria provide for two categories:

(1) Spikes, which include focal or generalized spikes, spike-and-wave complexes, or high voltage, slow sharp waves during the resting record or during hyperventilation;

(2) Focal or generalized slowing

A photoconvulsive response was subsequently added as a disqualifying factor in 1969.
Independent of these criteria published by LeTOURNEAU and MERREN (10) in "Aerospace Medicine", November 1973, the German Air Force Institute of Aviation Medicine in cooperation with the Institute of Neurology of the University of Munich, developed the following three EEG categories:

Category I:	Paroxysmal disturbances with SW complexes or spike-wave variants or the combination of slow and sharp waves. Paroxysm, as used here, means a sudden occurrence of waves with high amplitudes, the shape of which is distinctly different from that of the background activity. (Fig. 2)
Category II:	Theta waves, isolated or in groups, monomorphic or multiform, localized or diffuse.(Fig. 3)
Category III:	Generalized abnormalities with slow or irregular EEG activity and instable frequencies. (Fig. 4)

The above categories were published in "Aviation, Space and Environmental Medicine" in February 1975. As a rule healthy subjects showing paroxysmal EEG disturbances with spikes, spike-wave complexes, spike-wave variants or the combination of slow and sharp waves should not be permitted to fly.

Considerable differences of opinion exist in assessing the significance of localized or generalized slow waves.

The present publication reports on the experience gained with the above categories during the two-year period from January 1971 to December 1972. It is part of an attempt to re-evaluate all abnormal EEGs taken during initial flying fitness examinations covering the period from 1969 until the present in order to deduce more meaningful assessment criteria and to develop improved examination techniques.

Materials and Methods:
As already mentioned, the Bundeswehr requires a baseline-electroencephalogram (EEG) as part of the complete initial flying fitness examination.
The EEG recordings are made with the subjects in a semi-supine position in the waking state, augmented by using the following provocative techniques: hyperventilation for 4 minutes and, after returning to the baseline EEG, photic stimulation. It is comprised of a succession of single and double flashes at broken intervals and a continuous change in stimulation between 3 and 30 cycles per second. The eyes are closed during photic stimulation.

The EEGs were first traced with an 8-channel SCHWARZER-recorder, later on with a 12-channel-model constructed by the same company. 6 physicians were engaged in the evaluation of the EEGs. All of them had experience in EEG interpretation. 2 draftees were just about completing their training, 4 were fully qualified encephalographers. All EEG evaluations were computerized, and thus we were able to readily retrieve the data concerning borderline, abnormal,or pathological findings.

During the 2-year examination period from January 1st, 1971, through December 31st, 1972, there were 1132 applicants for flying training examined at the German Air Force Institute of Aviation Medicine. The neuro-psychiatric examinations at the institute were preceeded by examinations in the departments of selection psychology, ophthalmology, and ENT. As a result of the policy at that time, which eliminated these subjects from further examination in whom any deficiencies were found in these specialities, there were only 973 EEG examinations. This means that in 10.04 % (absolute number 159) of candidates no EEG recordings had been performed.

EEGs were done on healthy male adults with a median age of 23 years (minimum age 17, maximum 57 years) (Fig. 1). This wide distribution in year of birth can be attributed to several reasons: Older age groups were examined for flying fitness because of the activation of a new air force speciality, namely weapons system operators for the F-4 Phantom aircraft. Furthermore it was a policy that pilots who had not flown for a period exceeding 5 years had to undergo a new initial flying fitness examination. Also included in this study were foreign pilot applicants with a higher average age and some older examinees who merely wanted to obtain a jet passenger's permit.

Results:
Automatic data processing selected 6.3 % (absolute number 61) of the 973 EEG assessments as not being within normal limits. 3.7 % (absolute number 36) (Table I) had a bearing on the subject's flying fitness qualification. 1.95 % (absolute number 19) were permanently disqualified for flying ; 1 % (absolute number 10) temporarily disqualified and 0.7 % (absolute number 7) were restricted to flying prop aircraft on the basis of the EEG alone. The 36 EEGs which precluded examinees from flying or restricted their flying assignment have been reviewed and classified in three categories according to our criteria published in "Aviation, Space and Environmental Medicine", February 1975 (12).

All EEGs with paroxysmal disturbances have been listed under group I subdividing into paroxysms with spike-waves or spike-wave variants on one hand and simple paroxysms on the other (Table II). Paroxysm as used here means a sudden occurrence of waves with high amplitudes, the shape of which is distinctly different from that of the background activity. Spike-wave paroxysms were found in 0.72 % (absolute number 1) and paroxysms in 6.2 % (absolute number 6), altogether 1,34 % (absolute number 13) of the EEGsregistered in the examination period. Paroxysms, which were pronounced to a degree precluding the examinee from flying training, have been observed only once in a baseline EEG; mostly they were provoked by hyperventilation. They occurred 5 times during photic-stimulation and in 2 cases even seizures could be observed.

With one exception all examinees classified under category I have been assessed as being permanently unfit for flying. This single case was rated as temporarily unfit for flying because a clinical examination had been deemed necessary.
Category II is characterized by slow waves of varying degrees. 1.95 % (absolute number 19) of the EEGs were classified under this category. The assessment of these EEGs is far from being uniform, probably due to the differing experience of the evaluators. A few (absolute number 5) were rated as permanently unfit for flying, 7 were restricted to flying prop aircraft only and the remainder (absolute number 7) temporarily unfit for flying, pending clinical clarification.
Generalized abnormalities were found in 0.41 % (absolute number 4) of the applicants and grouped under category III. All of them were permanently disqualified.

Discussion:
Abnormal EEG findings in healthy individuals still pose a considerable problem. The examination of a large number of healthy people has already resulted in the definition of "normal variants" and in a more liberal EEG interpretation since that time. It could be demonstrated that several normal variants are hereditary. For example, there is proof that the so-called slow waves found in the occipital region were genetically determined. There is still a major group of subjects revealing EEG abnormalities, in which diagnostic methods of the present state of art fail to disclose the underlying cause. Moreover, there are no statistical records available as of this writing which would permit a forecast of the probability that the recorded abnormality will progress into a disease later on, for example within a 5- or 10-year period.

This study clearly shows, that in the majority of cases EEG abnormalities can be elicited by appropriate provocation methods. Consequently the present conventional EEG must be supplemented by more refined provocation techniques if we are to achieve better forecasts as to which subjects will withstand flying stresses. For this reason no EEG should be performed in aviation medicine without such supplementary techniques. This policy applies at our institute. Our EEG is routinely augmented by 4 minutes of hyperventilation and photic stimulation, as already mentioned. With the appearance of slow or irregular waves under hyperventilation this excessive breathing is repeated and the senso-mobile performance of the examinee is tested concurrently.

In order to assess the ability of examinees with EEG disturbances to transfer acoustic signals into motor performance, we have constructed a simple electrical device allowing indexfinger movements of the same rhythm as the acoustic signals to be recorded on the EEG graph.

Category II includes slow waves over the fronto-temporal regions of the brain which can be an indication for cerebral circulatory deficiencies. The inherent risk of recurrent functional disturbances in the sense of partial ischemic attacks under rare peak stress situations must be determined. The cerebral collateral blood flow can be examined by unilateral and bilateral compression of the vertebral and carotid arteries.(13)

Category III with generalized EEG abnormalities predominantly shows EEG alterations characteristic of juveniles, rare normal variants, and metabolic disturbances, e.g. hyperbilirubinemia. There is reason to believe that because of the difficulties encountered while interpreting such EEGs, all examinees falling under this category were permanently disqualified for flying training.

Standardization of new examination and evaluation methods certainly exceeds the capacity of a single laboratory, whose main responsibility is the routine recording of EEGs.
From an economical point of view - of utmost importance in these days - it is selfexplanatory that research on one and the same subject on a national basis should be avoided.
Every effort should be made to exchange information and to accomplish uniform examination and interpretation methods. In this manner we should arrive at figures of statistical significance. These in turn should enable us to determine the probability of a later disease eventually causing elimination from flying duty.

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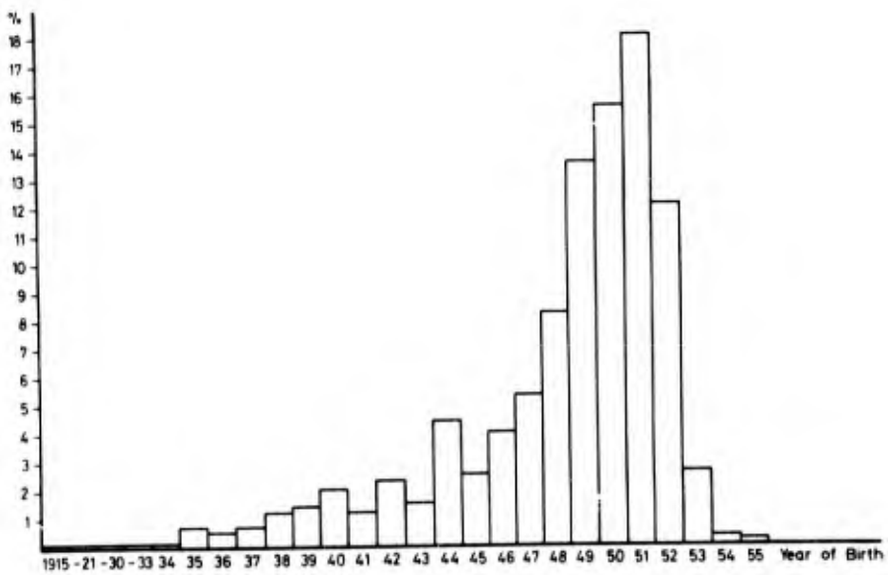

Fig.1 Distribution of examinees according to year and birth

TABLE I

Cases with EEG-Abnormalities having a Bearing on Flying Fitness and Breakdown into EEG-Categories

Number	Signature	Permanently Disqualified for Flying	Temporarily Disqualified for Flying	Flying Fitness for Prop. only	Permanently Disqualified in other Medical Fields	EEG-Category I	II	III
1971								
1	HO Ha	X					X	
2	SA Ha	X					X	
3	FR Wo	X				X SW		
4	IT Ha			X			X	
5	FA Pe	X						X
6	HE We		X				X	
7	PR Wo			X			X	
8	HU Wo			X	ENT		X	
9	CR Vo	X					X	
10	DO Wo		X			X P		
11	RU Al		X			X SW		
12	SE Al	X						X
13	KO Re			X			X	
14	GO Re	X				X P		
15	GR Kl		X				X	
16	HO Ge	X				X SW		
17	MA Ro	X					X	
18	OS Ha	X				A P		
19	IK Jo	X				X SW		
20	HO Ra	X				X SW		
21	HA Re	X				X P		
22	MO Eb		X				X	
23	ST Di	X					X	
24	NA Mi			X			X	
1972								
25	WO Jo	X				X P		
26	KU Ud			X			X	
27	MA Ha	X						X
28	WE Ge	X				X SW		
29	WE Ri	X					X	
30	SE Re		X		X-RAY DEPT.		X	
31	RE He		X			X P		
32	JA Sie		X				X	
33	SP Wa			X			X	
34	RI He	X				X SW		
35	WA Lo		X		INT		X	
36	HU Wi		X					X

Table I: Cases with EEG-Abnormalities having a Bearing on Flying Fitness and Breakdown into EEG-Categories

TABLE II

Breakdown of EEG-Category I according to Time of Onset of EEG-Abnormalities

Case-Number	SW Paroxysms	Paroxysms	Occurrence at rest	during Hyper-ventilation	during Photic Stimulation	Clinical Verification carried through yes	no
3	X			X	X	X	
10		X	X		X		X
11	X		X		X	X	
14		X		X		X	
16	X			X			X
18		X	X	X		X	
19	X			X			X
20	X			X			X
21		X		X		X	
25		X		X	X		X
28	X				X (fit)	X	
31		X			X		X
34	X				X (fit)		X

Table II Breakdown of EEG-Category I according to Time of Onset of EEG-Abnormalities

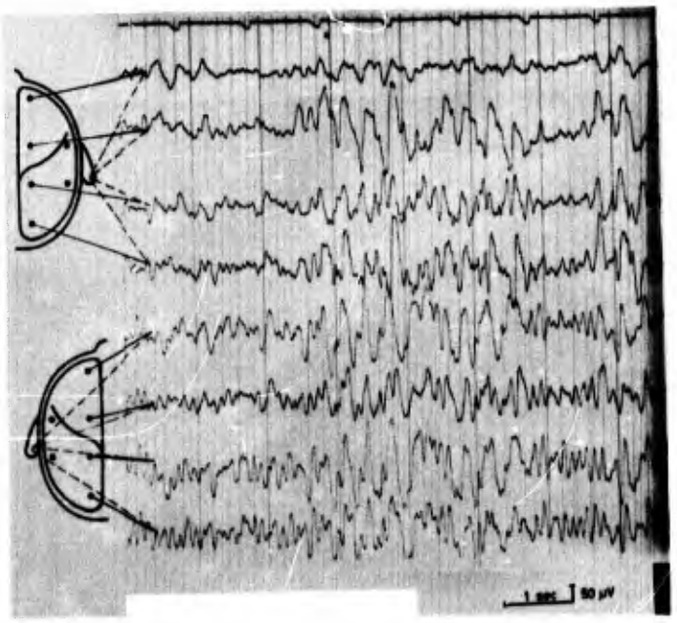

Fig.2 Example for EEG-category I

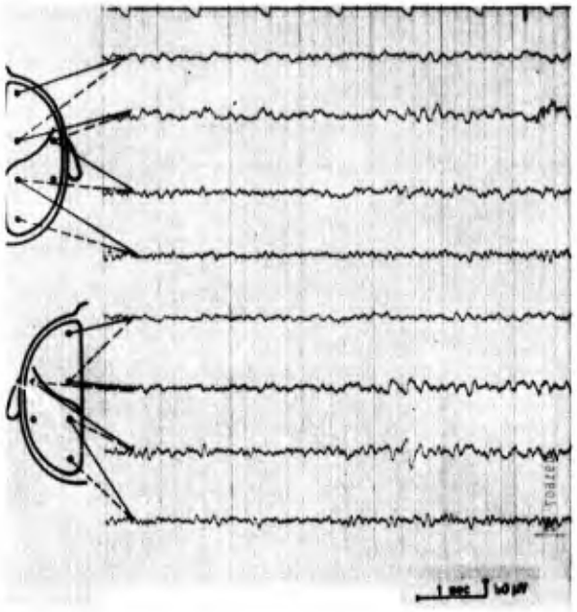

Fig.3 Example for EEG-category II

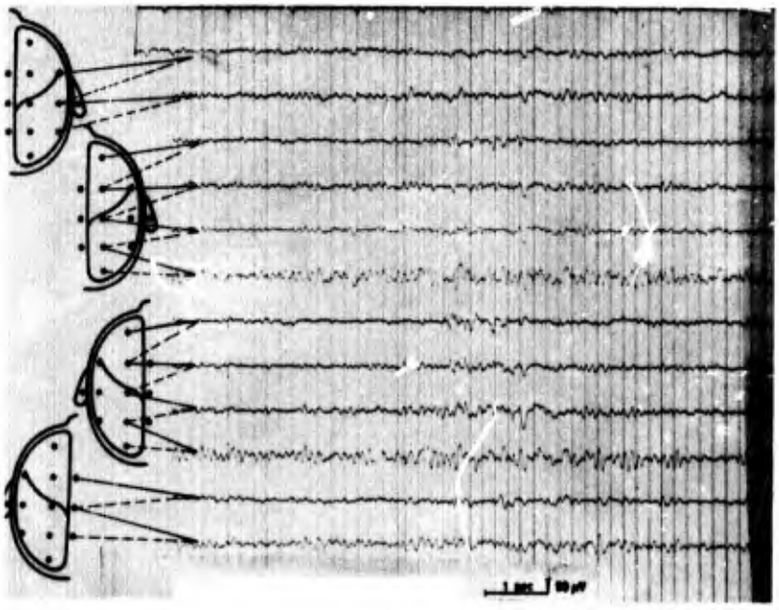

Fig.4 Example for EEG-category III

BEHAVIOUR OF SOME RESPIRATORY PARAMETERS IN CANDIDATE PILOTS. A COMPARATIVE STUDY BETWEEN TWO DIFFERENT GROUPS EXAMINED AT TEN YEARS INTERVAL

by

Col. C. A. RAMACCI, IAF MC Col. G. MEINERI, IAF MC

CENTRO DI STUDI E RICERCHE DI MEDICINA AERONAUTICA E SPAZIALE
(Director: Col. C. A. Ramacci, IAF MC)
Via P. Gobetti, 2A - 00185 Roma,(Italy)==

SUMMARY:

The hypothesis was advanced, by some investigators, that static respiratory values could undergo a change per se, in the course of time, in the same age-groups.

On this premise, a comparison was carried out between two groups of candidates to military piloting, submitted to physical examination, respectively in the years 1961-62 and 1971-72.

The respiratory parameters taken into consideration were: Vital Capacity, Timed Vital Capacity, other than their ratio (Tiffeneau's index).

The results show that — although a significative increase occurs in the 1971-72 group in regard to stature — no significative changes per se (i.e. non related to the aforesaid increase) could be put into light.

Thisnotwithstanding, it is still deemed advisable to perform periodical checks. In fact, the existence of other elements has been ascertained, that could be able, in the future, to exert a certain influence on the parameters at study.

INTRODUCTION:

In 1964 Rossanigo et al. carried on a remarkable investigation on some respiratory parameters in young Candidate Pilots.

These investigators concluded that none of the formulas (Anthony, Cournand, West, Baldwin, Ludwig, Cara, etc.), currently employed in the determination of the theoretical standard values of such parameters like Vital Capacity and Timed Vital Capacity, was fit to establish a standard value for comparison with actual measures recorded in the Italian Candidates.

Indeed experimental data differred to a large extent from the theoretical values derived from the abovementioned formulas, so that the latter could not afford an actual basis of judgement for the former.

Therefore, they proposed some new tables (but no formulas), accompanied by the corresponding nomograms, deduced from the statistical treatment of experimental data, recorded in more than 1000 subjects.

Since then, those tables are being employed in the attribution of a score to respiratory parameters recorded in Candidate Pilots, submitted to selection in the Italian Air Force, and also to Pilots submitted to control examinations.

Now, we asked ourselves whether these standards still hold good, after about one decade. In fact we deemed we could be authorized to think that possible changes had occurred in the anthropological constitution of young men. By the way, Scano et al., in a paper on psycho-physiological selection of Air Force Personnel, published in 1966, had expressed themselves in this way: "Vital Capacity shows, since 1953 and so far, an almost uninterrupted ascent, from mean values of about 4 lit. (1953 recordings) to more than 5.2 liters at present, therefore with a percentual increase of 30 per cent. Of such a fact is partly responsible the small increase of mean stature of the candidates, but, in our opinion, a greater part of it is due to some morpho-physiological characters of our subjects in relation to a more intense physical activity and better life conditions".

This implied the necessity of a continuous updating of evaluation standards in order to cope with possible new conditions, and testified the need of periodical elaborations of the data themselves, in order to adjust them to continuous or periodical changes of the parameters.

METHODS:

In the conduction of our work, we deemed it advisable not to compare directly the

most recent data at our disposal with Rossanigo's et al. values. (Besides, we do not have at our disposal, from Rossanigo's et al. paper, the theoretical equations on which they presumably based their conclusion).

Therefore we had rather to compare — independently from that work — two similar groups of candidate pilots (19, 20, 21 and 22 age groups), respectively submitted to psycho-physiological selection in the years I961-62 and 1971-72. Only after this preliminary investigation, we would have make a comparison between our data and the standard values contained in Rossanigo's et al. tables.

Of course, in the case that any possible augmentation of respiratory parameters could be attributed only to an increase of stature, there would be no need of modifying standard values. Therefore, it was absolutely necessary to distinguish between changes of mere statural origin and possible changes, due to different morphc-physiological characters of the candidates.

We had, therefore, to determine whether any change of mean stature had occurred. In fact, only after this, could we be able to put into evidence those possible changes, already mentioned, independent from stature increase.

Indeed, since the two parameters we have taken into consideration, are strictly and directly related to stature, any increase of mean stature of the groups should reveal itself in a variation of mean Vital Capacity and Timed Vital Capacity, which are the two respiratory parameters taken into consideration. But these changes would not be per se, that is to say related to morpho-physiological variations other than statural changes.

In the first table, we reported mean statures of the different groups of candidates, and of the two populations (i.e. 1961-2 and 1971-2) each taken as a whole, without keeping age grouping into account.

TABLE I (STATURE - cm -)

Age group	N	1961-62 groups	Age group	N	1971-72 group	Diff%
19	21	171.62±6.64	19	I69	173.96±5.59	+1.3
20	70	171.34±6.65	20	223	173.39±6.10	+1.2
21	120	172.03±5.67	21	234	173.59±5.54	+1.8
22	130	170.51±5.31	22	63	173.09±5.99	+1.9
19-22	341	171.30±5.75	19-22	689	173.61±5.66	+1.3

(Every increase in mean stature is statistically significative at less than 0.01)

At this point we could pass to the second phase of our elaboration, consisting in calculating the regression coefficient (r) and the theoretical equations, from which it would be possible to establish theoretical standard values of Vital Capacity (VC) and Timed Vital Capacity (TVC).

RESULTS:

The aforesaid calculations and equations are reported in the Tables II and III, and are graphically represented in figures 1 and 2.

From these tables and diagrams, we can observe that:

1) Linearity is always highly significative - between stature and VC and TVC (p less than 0.0I - with the exception of TVC in the 1961-62/19 years group, of too little consistency).

2) In general no peculiar difference can be detected between old and new values. This has been statistically proven thanks to the variance analysis of single corresponding statural groups.

3) A comparison with Rossanigo's et al. values shows that there is a satisfactorily good correspondance between their and our results.

Furthermore, we have also plotted theoretical VC against TVC, not keeping into consideration the parameter stature. Following this line of procedure, we have calculated the r and the theoretical equations, so that TVC can be deduced from VC. These equations are reported in tabls IV, while their graphic representation is given in fig. 3.

Also in this case linearity is fairly preserved. It is also confirmed that no significative difference exists between the "old" and the "new" groups.

Anyway a very accurate analysis put into evidence that a certain difference between the curves explained a particular behaviour of Tiffeneau's Index, which is different in the two series of groups.

T A B L E II - VITAL CAPACITY

Age group	1961 - 62	1971 - 72
19 Y	VC_{BTPS} = (60.90 x St.cm)-5365.30 r = 0.70 ± 0.16 p < 0.01	VC_{BTPS} = (72.34 x St.cm)-7311.81 r = 0.60 ± 0.07 p < 0.01
20 Y	VC_{BTPS} = (59.22 x St.cm)-5066.58 r = 0.65 ± 0.09 p < 0.01	VC_{BTPS} = (71.20 x St.cm)-7205.64 r = 0.56 ± 0.06 p < 0.01
21 Y	VC_{BTPS} = (79.92 x St.cm)-8595.01 r = 0.64 ± 0.07 p < 0.01	VC_{BTPS} = (65.11 x St.cm)-6117.99 r = 0.62 ± 0.05 p < 0.05
22 Y	VC_{BTPS} = (72.12 x St.cm)-7388.24 r = 0.66 ± 0.07 p < 0.01	VC_{BTPS} = (58.78 x St.cm)-4845.18 r = 0.52 ± 0.05 p < 0.01
19 - 22	VC_{BTPS} = (74.25 x St.cm)-7665.55 r = 0.65 ± 0.04 p < 0.01	VC_{BTPS} = (68.80 x St.cm)-6733.10 r = 0.61 ± 0.03 p < 0.01

T A B L E III - TIMED VITAL CAPACITY

Age group	1961 - 62	1971 - 72
19 Y	TVC_{BTPS} = (42.55 x St.cm)-3826.07 r = 0.36 ± 0.21 p > 0.05	TVC_{BTPS} = (54.24 x St.cm)-5046.69 r = 0.54 ± 0.06 p < 0.01
20 Y	TVC_{BTPS} = (41.60 x St.cm)-2873.33 r = 0.49 ± 0.11 p < 0.01	TVC_{BTPS} = (51.10 x St.cm)-4582.26 r = 0.60 ± 0.05 p < 0.01
21 Y	TVC_{BTPS} = (45.27 x St.cm)-3516.79 r = 0.41 ± 0.08 p < 0.01	TVC_{BTPS} = (44.06 x St.cm)-3379.48 r = 0.50 ± 0.06 p < 0.01
22 Y	TVC_{BTPS} = (49.86 x St.cm)-3137.51 r = 0.47 ± 0.08 p < 0.01	TVC_{BTPS} = (49.2 x St.cm)- 4189.92 r = 0.52 ± 0.11 p < 0.01
19 - 22	TVC_{BTPS} = (43.05 x St.cm)-3143.31 r = 0.45 ± 0.05 p < 0.01	TVC_{BTPS} = (49.80 x St.cm)-4338.65 r = 0.55 ± 0.03 p < 0.01

T A B L E IV - TVC VERSUS VC

Age group	1961 - 62	1971 - 72
19 Y	TVC_{BTPS} = (0.48 x VC)+ 1911.15 r = 0.61 p < 0.01	TVC_{BTPS} = (0.57 x VC)+ 1412.88 r = 0.62 p < 0.01
20 Y	TVC_{BTPS} = (0.63 x VC) + 1035.59 r = 0.79 p < 0.01	TVC_{BTPS} = (0.59 x VC) + 1233.73 r = 0.78 p < 0.01
21 Y	TVC_{BTPS} = (0.66 x VC) + 873.69 r = 0.78 p < 0.01	TVC_{BTPS} = (0.63 x VC) + 1021.86 r = 0.73 p < 0.01
22 Y	TVC_{BTPS} = (0.51 x VC) + 1624.35 r = 0.64 p < 0.01	TVC_{BTPS} = (0.56 x VC) + 1325.28 r = 0.71 p < 0.01

T A B L E V

CALCULATED TIFFENEAU'S INDEX

Stature cm	1961 - 62	1971 - 72
160	0.88	0.85
165	0.86	0.84
170	0.85	0.83
175	0.82	0.82
180	0.81	0.82
185	0.79	0.81
190	0.78	0.81

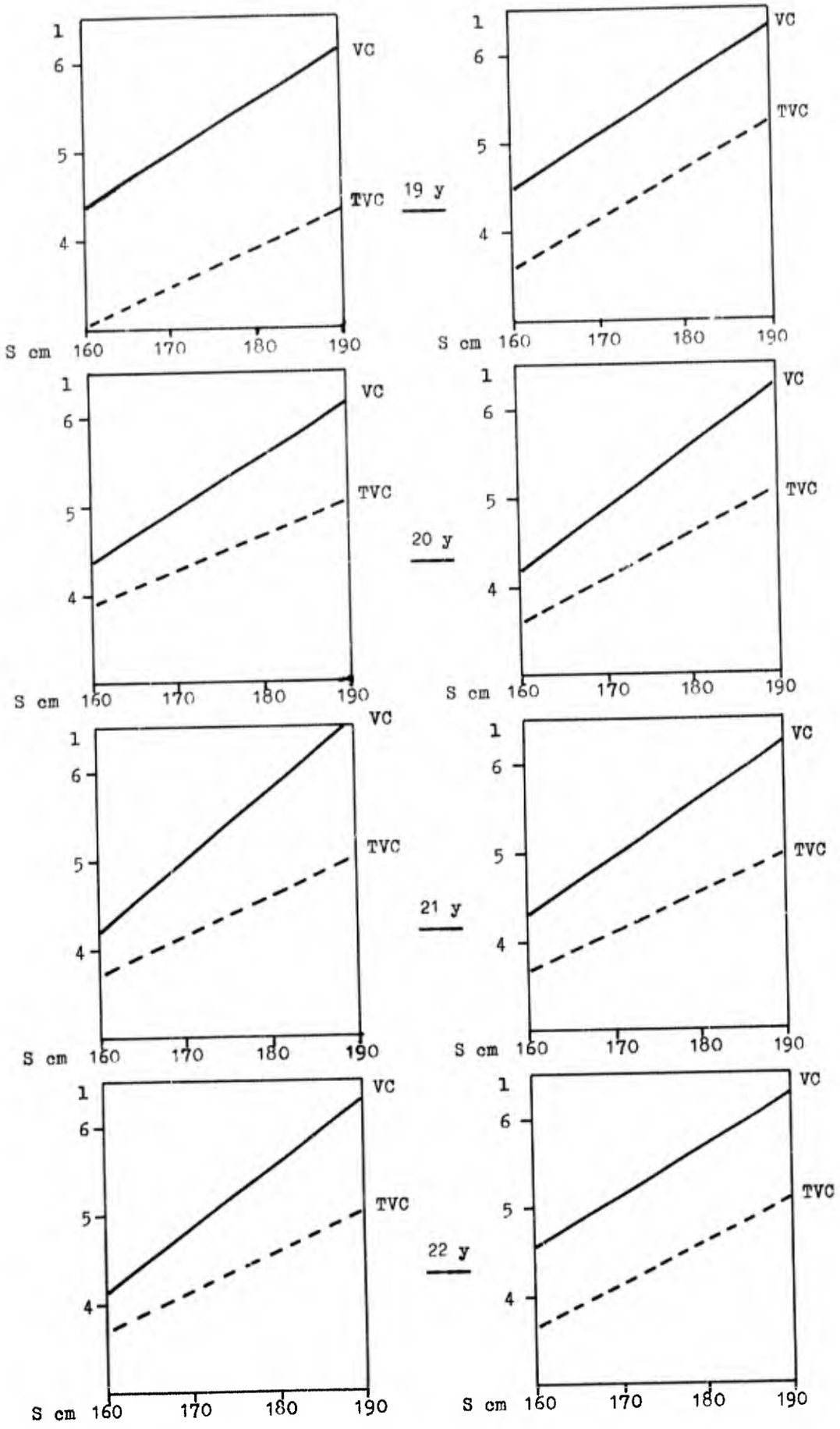
1
6
5
4
VC
TVC
S cm 160 170 180 190
19 y
20 y
21 y
22 y
1961 - 1962
1971 - 1972

Fig. 1

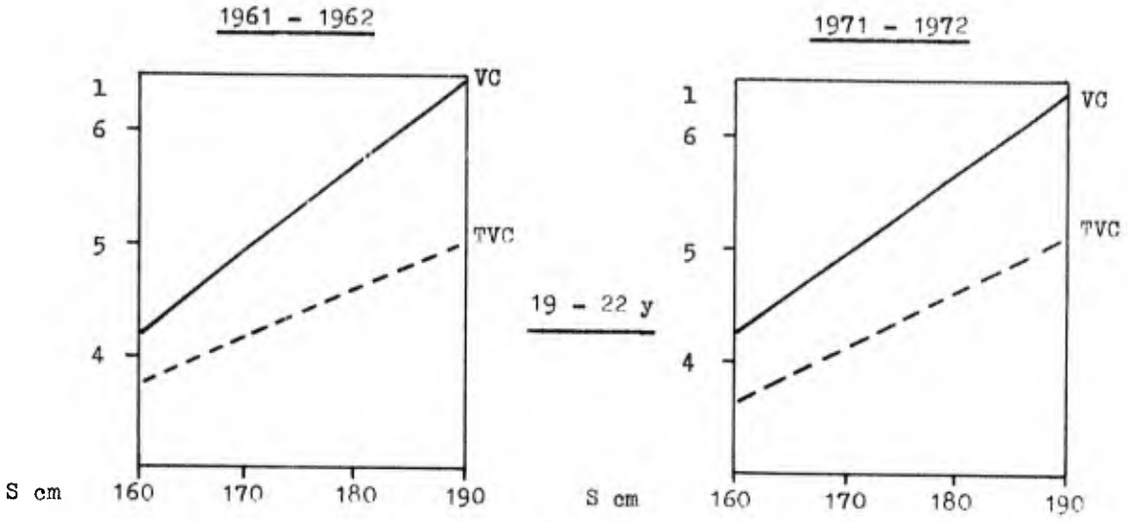
1961 - 1962
1971 - 1972
VC
TVC
1
6
5
4
S cm
160
170
180
190
19 - 22 y

Fig. 2

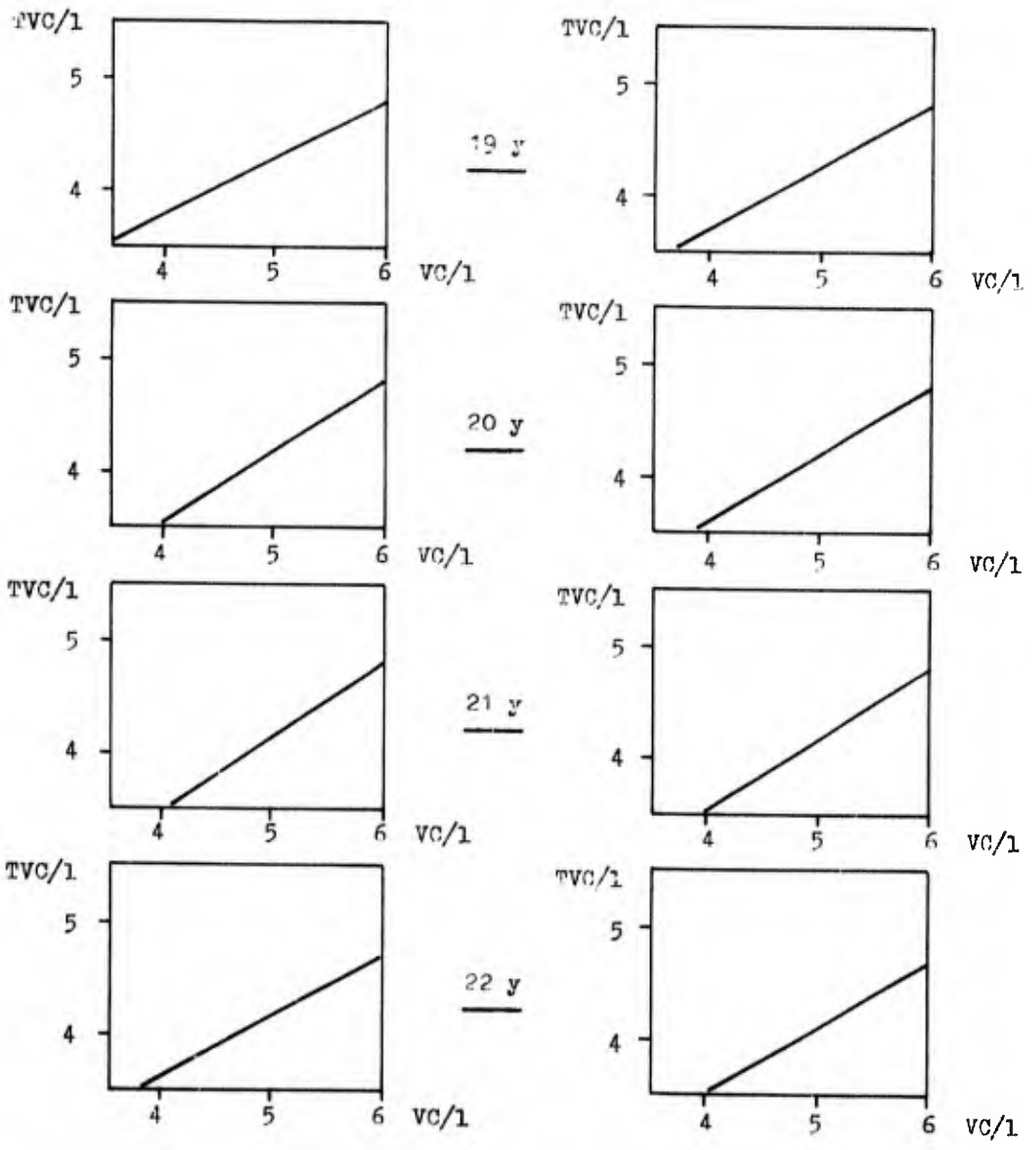
TVC/1
VC/1
19 y
20 y
21 y
22 y
4
5
6
1961 - 1962
1961 - 1962

Fig. 3

This behaviour is reported in table V. From it we can easily appreciate the well known reduction of the Index, proportional to the increase in stature. The phenomenon is clearly due to the fact that, if lung volume is higher in taller subjects, airways section is not enlarged in proportion; therefore resistance is increased to the expulsion of larger masses of air.

The higher values for the highest statural groups of I971-72 subjects, in comparison with the 1961-62 groups, could be explained with a modest improvement of athletic performance in the new generation. On the other hand it is not easy to explain the higher values, which, on the other hand, can be observed with the smallest statural values in the "old" generation.

For a clearer explanation of this phenomenon, it would be perhaps necessary to explore other morpho-physiological parameters, but we intend to treat this problem in a future work.

For the time being we have limited ourselves to determine the percentage of the dependency of VC and TVC from stature. This is very simply obtained by squaring the r and multiplying it per 100. In this manner we have obtained this table:

TABLE VI

Percentage of dependence of Vital Capacity from stature

I96I-62		I97I-72
49 %	I9y	36 %
43 %	20y	32 %
40 %	21y	38 %
44 %	22y	27 %
42 %	19-22y	37 %

This means that other factors (alimentary, athletic, morphophysiological, etc.) are acquiring a higher weight in the determination of VC. On the other hand TVC in "modern" subjects shows a higher dependency from stature, which we will not try to explain here.

CONCLUSIONS:

Our investigation was limited to the wish of complying with the advice of several researchers, in whose opinion, since they are possibly changing in time, physiological parameters should be periodically controlled, in order to ascertain whether any modification has occurred in them. Although we were not able to ascertain any really important change in VC and TVC, non depending from an increase of stature, we still maintain our opinion that periodical checks should be performed in the future. Indeed, the factors, not well specified, which, at present, show a certain trend to influence respiratory parameters, could be well acquire an important weight in the future. Anyway, for the time being, standard tables in use are still valable, since statural changes only cannot affect their validity.

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SURVEY ON MEDICAL REQUIREMENTS AND EXAMINATION PROCEDURES FOR THE PREVENTION OF TRAUMATIC AND NON-TRAUMATIC OSTEO-ARTHROPATHIES DUE TO FLYING ACTIVITIES.

by

Brig.Gen.Prof.Gaetano ROTONDO, IAF (M.C.)
Italian Air Force Medical Service H.Q.
Via P.Gobetti 2 - 00185 ROME - ITALY

SUMMARY.

The skeletal apparatus, and particularly the spine, is one of the most important localizations of the affections, especially traumatic, frequently observed in aviation pathology.

In view of this, the author examines and analyses the criteria, the medical requirements and the examination procedures which may be employed during the selection and the control of flying personnel, in order to point out all the anatomo-functional conditions facilitating the production of the osteo-arthropathies during the flying activity : in fact, since the bony framework and, above all, the spine undergo considerable mechanic strains during flying at high speed, the perfect integrity of osteoarticular system and spine in particular appears to be necessary from both anatomical and functional point of view.

There are many, often completely asymptomatic alterations of congenital or acquired origin which, if not especially looked for, can easily escape to routinary investigations and remain unnoticed until a revealing event occurs ; they play an important concausal role in the production of serious lesions as fractures, dislocations, spondylolisthesis and so on or, at least, are the cause of early unfitness to flight because of lumbago, ischialgia, discal prolaps, arthrosis and so on. Thus all the other potential conditions which are favourable to skeletal and vertebral injuries during flying activity, should be carefully investigated and detected prophylactically in aspirant pilots.

For the same reasons, also the pilots already on duty should undergo besides routinary control examination also a periodic systematic clinical and X-ray examination of the skeletal apparatus, especially of the spine, even at long intervals, in order to detect all acquired alterations, possible disregarded fractures being only one of the various aspects. Moreover, the ascertainment of all other important diseases of the osteoarticular system, as serious spondyloarthrosis, discopathies and so on, will make it possible for the physician to limit or control the further flying activities of pilot.

All these means should be valid and useful not only for the prevention of the traumatic and non-traumatic osteo-arthropathies of flying personnel, but also for the prevention of their subsequent early unfitness to flight.

INTRODUCTION AND GENERAL CONSIDERATIONS.

Fractures of the spine, either solitary or associated with other skeletal damage, are of great importance in Aviation accident pathology because the spine is one of the most important localizations of fatal and non-fatal traumatic lesions observed in aircraft accidents.

Apart from fatal injuries proving too serious and numerous so that no analysis can be performed, vertebral fractures appear to be the most frequent type of lesions of the spine occurring in non-fatal aircraft accidents, as was found by NEELEY and SHANNON (1958, 14). Also according to DUCROS and GREGOIRE (1954, 7) the frequency of the vertebral lesions is very high in the aircraft accidents occurred in French Air Force (respectively 42,5 per cent in the fatal cases; 11,5 per cent in the non-fatal cases).

Particularly, vertebral fractures occurring with some frequency following escape from aircraft by means of catapulting with ejection seat can be mostly regarded as "typical" because not only of the constant uniformity of their pathogenetic mechanism but also of their anatomo-pathologic substrate as well as corresponding clinical and radiological pictures.

In this particular field of Aviation pathology I have recently analysed (ROTONDO, 1974,22) the results of 100 cases of ejections, personally observed, and carried out by military and civil Italian jet-pilots in a long period of time (20 years). Forty-seven of this group successfully ejected from aircraft without injury and eleven ejections proved fatal. The remaining forty-two pilots sustained traumatic injuries after ejection, and of these fifteen sustained single or multiple vertebral fractures, while twenty-seven sustained other traumatic injuries different from spinal fractures. There were twenty-three vertebral fractures in fifteen pilots and the most frequently affected vertebrae were those of the thoraco-lumbar junction.

This selective and therefore typical localization of both single and multiple vertebral fractures after ejection can be explained by the particular anatomo-functional feature of the thoraco-lumbar passage tract of the spine. In fact, because of its function as a fulcrum of the double curve formed by thoracic kyphosis and lumbar lordosis it acts as a hinge-zone, endowed with considerable motility and functional activity, and is therefore particularly subjected to the hyperflexion movement sustained by the torso at ejection because of the acceleration-ejection jolt acting on the pilot in the direction buttocks-head. This is confirmed by the frequent deformation with anterior wedge-like squashing of the fractured vertebra.

If in Aviation accident pathology the most frequent spinal lesions usually prove to be the vertebral fractures, which are often observed in non-fatal aircraft accidents (and more often in fatal ones), it is possible sometimes to observe also other traumatic spinal lesions different from vertebral fractures, especially as effects of acrobatic flight and, above all, following the accelerations head-feet and the abrupt and repeated traumatisms, also if not very violent.

Numerous cases of luxations or ruptures of intervertebral disks have been described by many Authors, as CODE and coll. (1947,4), SHAW (1949,25), CICALA and ASSENSI (1956,3), and so on. I also have recently (ROTONDO, 1971,20) described and analysed a case of distortion of cervico-thoracic spinal tract, occurred to a jet-pilot during the acrobatic flight.

Obviously, since these lesions are not constant in all the pilots subjected to the same frequent stresses in the same conditions of flight, it is necessary to admit that their occurrence is favoured by a particular anatomical predisposition, such as a slight and not detectable anomaly of the intervertebral joints and/or an articular, congenital or acquired, ligament laxity.

But also if we don't take into consideration the traumatic vertebral lesions most frequently occurring in the flight accidents, the skeletal apparatus and particularly the spine appear to be the frequent localization also of non-traumatic osteo-arthropathies, often occurring in aviation pathology.

This has been shown by the results of a statistical survey, recently carried out (ROTONDO, 1971,21) on all Italian flying personnel who has undergone a medical examination during a period of six years at the three Aero-Medical Institutes of the Italian Air Force and for whom medico-legal measures of unfitness were taken for illnesses of any kind, physical and psychical, traumatic and non-traumatic.

In this way a study was made of the incidence - among flying personnel - of morbidity, or rather that part of morbidity that is the cause of unfitness ; and thus it was possible to indicate the diseases of the various organs and apparatuses that recur most frequently in determining both temporary and permanent unfitness for flying service.

Then in this statistical survey (where the morbidity was broken down into classes of illnesses according to the accepted international analytical classification), the second place among the most frequent causes of temporary unfitness for flight is occuped by the Traumatic Lesions due to "Accidents, Violence and Poisoning" (Group XVII of the above said International Classification), with 641 cases altogether (126 of which in pilots), accounting therefore for a percentage of 15,11 per cent of the total number of all the diseases of the various apparatuses (4243) making up all the multiple causes of unfitness, and for 24,76 per cent of the total number (2589) of cases of temporary unfitness evaluated.

Altogether there are 16 cases (including 5 pilots) in which there resulted permanent unfitness for military service and/or for flying ; therefore traumatic lesions take the sixth place among all affections causing permanent unfitness for flying service, with a percentage of 6,45 per cent of all the illnesses of the various organs leading to permanent grounding.

Immediately following the traumatic lesions, the third place among illnesses constituting the most frequent causes of temporary unfitness for flight is taken by "Diseases of the Bones and of the Organs of Locomotion", with 528 cases in all (including 137 in pilots), accounting therefore for a percentage of 12,44 per cent of multiple causes of unfitness, and for 20,40 per cent of the total number of subjects suffering from temporary unfitness.

The cases in which permanent unfitness for military service and/or flying resulted from the illnesses of this Class (Group XIII of Analytical International Classification) amounted in all to 40 (including 15 pilots). It is seen, therefore, that diseases of the Osteoarticular System occupy the second place among all causes of permanent unfitness for flying service, accounting for a percentage of 16,05 per cent of all the illnesses of the various apparatuses that led to permanent grounding.

As regards the relative frequency of the various osteoarticular diseases, the survey has shown the vast majority of arthrosic forms, particularly spondyloarthrosis (58,5 per

cent of the total number of all the illnesses of the Bones and Organs of Locomotion), and of forms of rheumatoid arthritis and arthromuscular rheumatism (30 per cent) ; a long way behind, osteomyelitis and other diseases of the bones and joints (9,3 per cent) come next, followed by the other affections of the osteomuscular system, such as borsitis, arthrosinovitis, tenosinovitis, myositis etc. (2,2 per cent).

Such a relatively high frequency of arthrosic, arthritic and rheumatic affections in general, which occupy the second place among all illnesses causing permanent grounding and the third place among those causing temporary unfitness among aircrew, induce us to make here some clinical and medico-legal considerations that are concerning both occupational medicine and aviation medicine at the same time.

It has been well known that prolonged exposure to unfavourable environmental and climatic conditions, to perfrigeration, to physical discomfort, to repeated and localized microtraumas, and to irrational and incongrous positions of the body at work, encourage and accelerate the pathogenesis, evolution and clinical course of arthroreumatic affections in general. The specialist personnel working daily on the flight line of the Air Bases, nearly always in the open air, in all seasons and in any weather, and exposed therefore to all the inclemencies and vagaries of the seasons, certainly cannot escape this influence. Pilots and aircrews are exposed, in addition to the above-mentioned factors, also to the unfavourable effects of the repeated and frequent variations of temperature, humidity and barometric pressure that flying inevitably involves.

All that explains why illnesses of the osteoarticular apparatus are rather frequent in aircrews, even apart from the results and consequences of any traumatic injuries that take place at work in the course of service and which quite frequently lead to post-traumatic arthropathies.

In flying personnel, moreover, some phlogistic or degenerative affections of the joints, originating in some other causes, may be aggravated by flying, and some may even be brought about and produced by conditions that emerge during and as a result of flying, such as for example aeroembolism (or decompression sickness) and vibrations. It cannot be excluded that these factors may give rise, with repeated exposure, to arthropathies similar to degenerative chronic arthrosis due to cofferdam disease and to osteoarthropathy due to vibrating agents, with the mechanism of the embolic stoppage of the little vessels that nourish the articular extremities and consequent phenomena of subchondral necrosis in the first case, and with the production of cartilaginous microlesions and subsequent osteophytic degenerative and reactive phenomena in the second case.

All the etiopathogenetic considerations mentioned above can give us a sufficient explanation of the frequency, which is relatively considerable, with which diseases of the osteoarticular system recur and have been observed among Air Force personnel.

METHODS AND DISCUSSION.

The above-mentioned considerations on the statistical incidence, pathogenesis, as well as important aeromedico-legal aspects (with the relative consequences, often causing unfitness) of traumatic and non-traumatic osteo-arthropathies, which frequently recur in Aviation pathology, now prompt us to take into proper consideration also the preventive aspects of these affections of the osteoarticular system, which sometimes can play - in the flying personnel - the role of occupational diseases.

Particularly it may be very interesting and very important to research and to study some preventive aeromedical means, which could be able to reduce the frequency of the traumatic vertebral lesions, often recurring in flight accidents and especially in ejections : in fact, these professional injuries ought to be largely reduced or completely eliminated from aviation accident pathology, in order to avoid the serious effects and results they may sometimes have owing to the compression and impairment of nervous plexuses or important nervous formations.

In view of this it is useful for us to examine and analyse now the criteria, the medical requirements and the examination procedures which may be employed during the selection and during the successive periodic controls of flying personnel, in order to point out all the anatomo-functional conditions facilitating the production of the osteo-arthropathies during the flying activity. These means can be regarded as useful and necessary for the prevention of the above-mentioned osteo-articular diseases.

In my opinion, there are different means on which prevention can be based.

First of all, I think that the spines of all aspirant military pilots (especially fighter pilots) should be submitted - obviously, after and besides the preventive complete clinical examination - to a careful X-ray examination at preliminary selection in order to eliminate those subjects who, affected by some - also slight and asymptomatic - vertebral injuries or malformations, could be the most probable or certain candidates for the traumatic spinal lesions in the case of aircraft accident, and ejection in particular.

In fact, since the bony framework and, above all, the spine undergo considerable mechanical strains during flight at high speed, the perfect integrity of the osteo-ar

ticular system and of the spine in particular appears to be necessary both from the anatomical and from the functional point of view.

There are many, often completely asymptomatic alterations of congenital or acquired origin which, if not especially looked for, can easily escape to routinary investigations and remain unnoticed until a revealing event occurs ; they are playing an important concausal role in the production of serious injuries such as fractures, dislocations, spondylolisthesis and so on or, at least, are the cause of early unfitness to flight because of lumbago, ischialgia, discal prolaps, arthrosis and so on.

For instance, even simple abnormalities of vertebral position such as kyphotic, scoliotic and lordotic deviations can contribute to the production of spinal fractures by hyperflexion. Under these conditions, in fact, the flexing forces are noticeably increased owing to the uncongruent position of the chest as regards the load axis with resulting increase in inert mass. Moreover, in such attitudes at the limits of the normal the discal apparatus is not in its best conditions to exert its action of force reduction.

Also degenerative alterations of limiting laminae which may even form intraspongious herniae, as well as actual discopathies or their results, are very important in the case of considerable strains such as during ejection or in particular acrobatic phases of supersonic flying. In these cases, and under particular conditions, the impairment of one of the damping systems brings about a locus minoris resistentiae more exposed to traumatic action.

Other conditions which predispose to traumatic injuries of the spine are spondylolysis and spondylolisthesis, often undetected : in ejection the very high acceleration acting on the spine finds, at level of the listhesic section, a highly favourable anatomic condition for the production of very serious traumatic injuries.

Finally, all deformations of the spine, fissurations of vertebral body and arch, congenital disco-somatic alterations such as congenital vertebral synostosis, transition anomalies such as sacralization of L.5 and lumbarization of S.1, structural anomalies of vertebral bodies such as wedge-like vertebrae, results of osteochondritic processes not detected in childhood, results of previous unknown vertebral fractures, vertebral angioma (usually asymptomatic) and all congenital or acquired trophic alterations of paravertebral muscles can be further conditions highly favourable to vertebral injuries during flying activity. An effort should therefore be made to investigate carefully and to detect prophylactically any such conditions in aspirant pilots, in order to have the possibility of evaluating, case by case, if the nature and extent of these alterations make it necessary to eliminate the subjects during the preventive selection.

Obviously, it will be possible to detect the above-mentioned congenital or acquired vertebral anomalies if all subjects examined will undergo not only a careful preventive clinical examination (which may, in the first place, show any abnormalities of postural vertebral position), but also - and above all - a complete X-ray examination of the spine.

This radiological examination in aviation medicine does not differ from that for any other spinal injury in general Orthopedy, and will be performed in order that the entire spine must be X-rayed both by antero-posterior and by lateral views rispectively in the cervical, thoracic and lumbar-sacral sections. If necessary, this examination will be completed with the tomography of L.5 by antero-posterior view and with the dynamic exploration by lateral view for the eventual study of any congenital anomalies (AUFFRET and DELAHAYE, 1972,1).

Besides, all spinal anomalies call for the use of localised X-rays (AP and lateral) in which attention must be paid to the roles of angles of incidence by approaching the examination of each segment via its concavity and by adapting the technique to the needs of each particular case. Lateral views will enable one to calculate precisely the correct incidence for the localised plates.

The examination of a posterior arch in the lumbar region can be made at angles of incidence from 3/4 right or left and at an angle of 45° to the plane of the posterior articular processes in the median sagital plane. At the thoracic level, the fact that the posterior articular facets are on the horizontal plane, calls for the use of lateral view tomograms (DELAHAYE and coll., 1970,5).

The practical execution of the systematic obliged vertebral X-ray examination procedure in all aspirant military pilots, already in experimental phase in Italian Air Force, is giving very good results since it has been thus possible to detect and eliminate, during preventive selection, numerous subjects who were affected by important spinal dismorphisms and other vertebral anomalies.

For the same reasons described above, also the military pilots already on duty should undergo, in addition to routine control examinations, also a periodic systematic clinical and radiological examination of the spine, even at long intervals, in order to detect all acquired alterations, possible disregarded fractures being only one of the various aspects.

Moreover, the ascertainment of all other important diseases of the osteo-articular system, such as serious arthrosis, discopathies, and so on, will make it possible for the physician to limit, stop or control adequately the further activity of the pilot.

A complete and systematic X-ray examination of the spine, including the tomographic one and, if necessary, the radiodynamic study (in anterior or lateral flexion), is also necessary - for an immediate diagnosis and treatment in the first place, but also for the prevention of any further traumatic accidents - in the case of flying personnel who have been subjected to particular strain as the result of aircraft accidents, especially after parachuting or violent landing, in order to detect the presence of any vertebral injuries, which sometimes may not present any symptoms.

For instance tomograms, both antero-posterior and lateral, enable one to make a fine and minute examination of the lesions as well as of the posterior wall of Rieunau. Antero-posterior tomograms particularly in the lowest posterior planes are useful since they ensure an almost complete exploration without having to move the patient out of his supine position.

In certain cases with simple compression, a dynamic radiological examination enables one to assess the degree of mobility of the spine, any variation in the shape of the intervertebral spaces, and thereby confirm the presence or absence of injury either of the inter-spinal ligament (widening of the space between the spinal processes) or of the disks (pinching or selective widening). This radiodynamic exploration makes use of antero-posterior views with lateral right and left flexion and lateral views with flexion and extension (DELAHAYE and coll., 1970,5).

Thus the X-ray examination, performed with the above-described technique and supplemented by eventual localized radiograms, stratigraphies etc., makes it possible to localize the seat or the seats of fracture and to obtain a profile of discal injuries also showing whether the interspinous ligaments and intersomatic disks are uninjured or not, and giving useful indications for therapeutical treatment and prognostic judgment on restitutio ad integrum and on functional and operative recovery of the subject.

Obviously, also the subsequent periodic control examination, particularly the X-ray one, will be generally very useful and interesting, if it is carried out every year for all pilots who have sustained vertebral injuries, even many years afterwards. It makes it possible to study and follow the evolution of the process of recovery of vertebral or discal-vertebral fractures and to evaluate the nature and extent of the long-term results of spinal injuries caused by flight accidents.

These long-term results, in the cases which have been examined in the Aeromedical Institutes of Italian Air Force and described and analysed by ROTONDO (1974,22), did not prove to be serious in general, not preventing the subsequent resumption of flying fitness; from the radiological point of view they can be classified among spondyloses and spondylo-disk-arthroses following trauma, of varying severity according to the type and location of the injury.

In particular, in the most frequent case of wedge-like vertebral fractures, where there is nearly always a disk-vertebral injury because of the laceration of the intersomatic disk above the anterior part of the vertebra that subsided under the pressure, repair processes often produce osteophytosic bridges with sclerotic disk-vertebral reaction and possible ossification also of the longitudinal ligaments, especially the anterior one, with further stabilization of the results of vertebral fracture and re-establishment of a sufficient static-dynamic balance.

At any rate, these periodic clinical and radiological control examination can be considered very useful as they make it possible to investigate the long-term evolution of the results of vertebral injuries and to take any therapeutical and medico-legal measures that are necessary.

CONCLUSIONS.

On the basis of all the above-mentioned considerations and of the experience being acquired in this preventive field of aviation medicine, I think we can come to the conclusion that the careful, constant and systematic execution of clinical and X-ray examinations of the skeletal apparatus, above all the spine, if performed during the selection and also during periodic medical controls of flying personnel, will make it possible to get numerous advantages, such as : the preventive elimination of all subjects affected by serious osteoarticular lesions which are susceptible to modify the skeletal - especially vertebral - resistance, and are not compatible with flying activity ; the possibility of performing useful comparative controls with other medical examinations performed before eventual traumatisms (ejections, flight accidents, and so on) ; and, finally, the careful and systematic study of occupational pathology of flying personnel.

The execution of this examination procedures for the ascertainment of the above-mentioned medical requirements, together with the systematic medico-legal study of these professional injuries and diseases and of the biodynamic mechanism of their production, are certainly means which will prove to be valid and useful for the prevention of the traumatic and non-traumatic osteo-arthropathies directly or indirectly due to flying activity, for the reduction of their harmfulness which still remains quite high in Aviation morbidity and pathology, and also for the prevention of the subsequent early unfitness to flight.

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CONTROL OF HEMOSTATIC DISORDERS IN AIR FORCE PERSONNEL

Dr. G. BLUNDO; Lt.Col. G. PAOLUCCI IAF MC; Lt.Col. P. ROTA IAF MC
Centro di Studi e Ricerche di Medicina Aeronautica e Spaziale
Via P. Gobetti, 2/a
00185 ROMA - Italy

SUMMARY

A general examination is carried out to establish the risk from possible hemostatic disorders, due to diseases, drugs or toxic industrial products, of subjects occupationally exposed to traumatisms, as Air Force personnel.

The study was performed on young people applying for enrolment in the Air Force, on healthy personnel in contact with solvents, lubricants and paints, and on healthy personnel with no such contact.

The hemostatic process was examined by studying partial thromboplastin time, prothrombin time, thromboelastographic record, platelet count and individual anamnesis.

The data obtained were discussed with respect to frequencies of hemostatic disorders found, and the utility of laboratory control in medical examination.

INTRODUCTION

Air Force personnel, because of its peculiar professional activity, is exposed both in flight and on the ground, to a frequent risk of traumatic lesions. In this occasion, normal hemostatic process can contribute to the diminution of the damage.

On the other hand, the hemostatic process can be affected by different causes, congenital and acquired. In particular, a few of them such as toxic ones, could be important for Air Force personnel in contact with solvents, lubricants and paints.

METHODS AND RESULTS

In view of the above considerations, we evaluated the hemostatic process in a group of healthy subjects, in submitting them to periodic medical examinations. The study was carried out on 101 subjects, divided into the following three groups :

1) 26 subjects undergoing their first medical examination for Air Force enlistment or civil pilot licensing, aged between 20 and 40 (average age 26).

2) 28 subjects in service in the Air Force including technicians in contact with solvents, lubricants and paints (engineers, assemblers, car drivers and mechanicians, fuel service staff) aged between 20 and 62 (average age 48).

3) 47 subjects in service in the Air Force, not in contact with the above toxic products (military pilots, air traffic controllers, electricians, office staff) aged between 20 and 65 (average age 45).

All the subjects examined were submitted to careful anamnesis, specifically with respect to individual and family records of hemostatic disorders, service history, drug consumption, previous diseases.

We found no evidence of family or individual records of hemostatic disorders, and all the subjects were fit for their own professional activity.

The hematological control carried out in this study was aimed at obtaining a general evaluation of the hemostatic process; it was performed on venous blood specimen in order to facilitate the routine examination (1).

Venous blood was diluted 9 to 1 with anticoagulant (sodium citrate). Quick time, partial thromboplastin time (PTT), thromboelastographic parameters and platelet numbers were recorded. All these data can demonstrate, as is well known, the thrombocytic phase of hemostasis, factors of coagulation and fibrinolitic phenomena (2).

In the table, on the next page, are reported average values and standard deviations of thromboelastographic parameters (3), Quick time, PTT, platelet numbers per cmm, in the whole and in the three groups.

	Thromboelastogram r mm	k mm	ma mm	Quick time sec.	PTT sec.	Platelets /cmm
Whole	14.98	4.30	57.57	16.23	32.52	409446
s	4.18	1.56	11.86		3.01	120.67
Grp.1	15.81	3.83	61.95	18	32.96	401710
s	3.55	1.18	9.15		2.76	62.29
Grp.2	13.75	4.30	56.00	16.30	32.20	410300
s	4.07	1.69	12.63		3.11	105.31
Grp.3	15.31	4.50	56.50	16.10	32.50	402600
s	4.45	1.62	12.26		2.92	137.45

In comparing these data, the following points should be considered :

1) Quick time was carried out with thromboplastin of two different firms, because of difficulties with supplies;

2) In a few subjects, because of technical difficulties, we were not able to carry out all the tests in the program.

The data obtained from the tests, both in the whole, and in the three Groups, can be considered within the normal ranges, as quoted in the literature and in the experience of this laboratory. The differences reported in Quick time for Group 1 is due to the different thromboplastin being used. Because of this, we do not report in the table the standard deviation for this test.

The data concerning platelet numbers, PTT and thromboelastographic parameters, show differences not statistically significant among the three groups, with the exception of the r value which is shorter in Group 2, and a ma value longer in Group 1. We think that the differences are probably due to unhomogeneity of the Groups, in respect to their age, and in any case they do not indicate any hemostatic trouble in Group 2 when exposed to toxic agents.

Among the 101 subjects studied we found three individuals, one in each group, showing hemostatic disorders, referred to thrombopenia. In subsequent examinations, carried out three months later, the hemostatic process was normal. In all the three cases observed, the hemostatic disorder found is probably related to the use of antineuralgic drugs.

CONCLUSIONS

We feel, from the above quoted data, that taking into account the limited number of subjects studied :

1) the frequency of hemostatic disorders in the personnel examined is very low, about 3%, and is demonstrated only with laboratory methods, without any clinical signs;

2) there was no evidence of effect of professional factors on hemostatic disorders;

3) the hemostatic disorders found in three subjects were transitory and probably related to drug use.

We conclude, on the basis of the present survey, that no useful purpose would be served by the routine examination of Air Force personnel for hemostasis.

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EVALUATION DE LA DISTENSIBILITE VASCULAIRE, DU DEBIT CARDIAQUE, ET DE LA CHRONOLOGIE CARDIAQUE, PAR LA MESURE DES VARIATIONS D'IMPEDANCE ELECTRIQUE THORACIQUE.

Médecin en Chef J. COLIN, Professeur Agrégé du Service de Santé des Armées,
Médecin en Chef J. DEMANGE, Professeur Agrégé du Service de Santé des Armées,
Médecin Principal J. LANGLOIS, Assistant des Hôpitaux des Armées.

Ecole d'Application du Service de Santé pour l'Armée de l'Air
5 bis avenue de la Porte de Sèvres - 75015 PARIS -
France.

RESUME

Les variations d'impédance électrique recueillies au niveau d'électrodes placées sur la face antérieure du thorax, en regard de l'aorte ascendante, sont proportionnelles aux variations de volume des vaisseaux thoraciques passant dans cette zone. L'étude de l'influence de l'âge sur les caractéristiques des tracés obtenus sur 91 sujets sains indique que les modifications des variations d'impédance sont en partie dues à des modifications de la distensibilité des vaisseaux sanguins.

Les enregistrements de variation d'impédance électrique thoracique ont également été utilisés pour évaluer le volume systolique et le débit cardiaque. La méthode a été calibrée par les résultats de 120 mesures simultanées par méthode de dilution et par impédance électrique sur des sujets cardiaques. Les valeurs obtenues sur les sujets sains sont en bon accord avec celles obtenues par des auteurs ayant utilisé la méthode de FICK, en particulier en ce qui concerne l'action de l'âge et de la position. La corrélation médiocre entre les méthodes de dilution et d'impédance électrique médiastinale haute chez les cardiaques rend cette méthode pour le moment difficilement utilisable en clinique, mais les résultats obtenus sur les sujets sains montrent que cette méthode, facile à mettre en oeuvre, et permettant des mesures de longue durée, est utile en physiologie aérospatiale.

I - INTRODUCTION

La nécessité de procéder à des investigations cardio-vasculaires dans des conditions de contraintes aéronautiques difficiles a amené le Laboratoire de Médecine Aérospatiale du Centre d'Essais en Vol de Brétigny-sur-Orge à rechercher des méthodes non sanglantes d'évaluation des débits sanguins périphériques (cerveau, membres) et du débit cardiaque.

Parmi ces méthodes, celles utilisant la mesure des variations d'impédance électrique ont retenu l'attention en raison de leur facilité de mise en oeuvre et de la possibilité de procéder à des mesures de longue durée.

L'utilisation des variations d'impédance électrique pour la mesure des variations de volume d'un segment corporel remonte à une quarantaine d'années, mais ce n'est que récemment que la pléthysmographie électrique a été proposée pour mesurer les débits sanguins, et notamment le débit cardiaque.

Sous la forme proposée initialement par KUBICEK et Coll. en 1966 (19), qui utilise les variations d'impédance du thorax entier, cette méthode a fait l'objet d'assez nombreuses publications. C'est ainsi que dès 1968 la NASA publiait un rapport de 468 pages, groupant les résultats de 24 équipes de recherche (20). C'est une méthode un peu différente qui a été utilisée par le Laboratoire de Médecine Aérospatiale.

Pour éviter la modulation importante du signal d'impédance par la respiration, inconvénient de la méthode de KUBICEK, DEMANGE et coll. ont proposé (5) de placer les électrodes de recueil en regard de l'aorte ascendante. C'est l'utilisation de cette dernière méthode, dite pléthysmographie électrique médiastinale haute, qui fait l'objet du présent travail.

Après un rappel de la méthode utilisée, nous étudierons l'influence de l'âge sur les variations d'impédance électrique (l'âge diminuant la distensibilité vasculaire, il a été recherché si cette dernière agissait sur l'impédance électrique), puis les possibilités d'évaluation du débit cardiaque. En même temps, nous verrons que l'enregistrement des variations d'impédance électrique thoracique permet l'étude de la chronologie des événements cardiaques.

2 - METHODE ET MATERIEL

La méthode de mesure d'impédance retenue a été celle, dite à quatre électrodes, préconisée par la majorité des auteurs (10 - 11 - 18 - 19 - 22).

L'appareil utilisé est un pléthysmographe électrique Diacardyne (x).

Deux électrodes servent à injecter le courant et deux électrodes à recueillir sur la peau la différence de potentiel créée par l'impédance corporelle.

Les deux électrodes d'injection de courant sont constituées par des bandes d'argent de 1/10 mm d'épaisseur, 15 cm de long et 1 cm de large, fixées horizontalement sur la peau à l'aide d'un ruban adhésif. L'une de ces électrodes est placée sur la face antérieure de la base du cou. L'autre est placée sur la face antérieure de la base du thorax, en-dessous de la pointe du coeur. Le Diacardyne injecte dans le corps, par ces électrodes un courant imposé de 100 KHZ, 0,9 m A.

Les deux électrodes de recueil sont similaires, mais de 10 cm de long seulement. Elles sont placées horizontalement et parallèlement l'une à l'autre, sur la face antérieure du thorax, en face de l'aorte ascendante. La distance séparant les bords externes de ces électrodes variait de 2,8 à 3,7 cm. Leur position a été contrôlée radiologiquement. Le plus souvent l'électrode supérieure était placée au niveau du bord supérieur du deuxième espace intercostal gauche (1,8).

(x) Société I.E.R.A.M., 31 rue de Chabrol, 75010 PARIS, France.

Ces deux électrodes recueillent la différence de potentiel existant entre les deux surfaces équipotentielles qui passent à leur niveau. Ces deux surfaces, perpendiculaires aux lignes de courant allant d'une électrode d'injection à l'autre, interceptent l'aorte, l'artère pulmonaire, la veine cave supérieure et du tissu pulmonaire (figure 1).

Les variations de la quantité de sang que contiennent ces vaisseaux entrainent des variations de leur conductivité (10, 11, 19, 22). Les variations d'impédance observées au cours de la systole cardiaque sont donc proportionnelles aux variations de volume de ces vaisseaux.

Du fait de sa proximité des électrodes de recueil, de sa forte pulsatilité et de sa position parallèle aux lignes de courant, l'aorte semble responsable de la majeure partie des variations de conductivité, donc des variations de la différence de potentiel entre les surfaces interrogées par les électrodes de recueil. Ce point n'a cependant pas reçu, jusqu'à présent, de justification expérimentale. D'autre part, les surfaces équipotentielles s'écartant l'une de l'autre à mesure que l'on s'éloigne du plan des électrodes de recueil, et leur disposition échappant à toute possibilité de calcul, la longueur des vaisseaux interrogés n'est pas connue et varie vraisemblablement d'un sujet à l'autre.

Cependant, bien qu'il apparaisse difficile de transformer les variations d'impédance en variation de volume, ces deux paramètres étant étroitement liés, il semble possible d'évaluer indirectement l'amplitude des variations de volume par les caractéristiques de l'enregistrement des variations d'impédance (c'est-à-dire les caractéristiques du pléthysmogramme électrique).

3 - PROTOCOLE

Le pléthysmogramme et le phonocardiogramme ont été enregistrés simultanément sur 91 sujets masculins au cours de leur visite médicale d'aptitude au personnel navigant, au Centre Principal d'Expertise Médicale du Personnel Navigant (dans le service du Professeur Agrégé CARRE).

Ces sujets, dont l'âge variait de 19 à 64 ans étaient tous aptes. La visite avait lieu le matin, à jeun. L'enregistrement était effectué sur les sujets au repos assis et, pour 19 d'entre eux, également en position couchée.

Les tracés étaient caractérisés par les 6 paramètres suivants : (voir figure 2)

- Zo, l'impédance de base par unité de distance inter-électrodes (bord externe à bord externe) en Ω/cm.
- ΔZ, la variation d'impédance maximum observée au cours de la systole, en Ω/cm.
- dZ/dt, la vitesse maximum de variation d'impédance au cours de la systole, c'est-à-dire l'amplitude maximum de la dérivée, en Ω/cm.s.
- RR, la période cardiaque, c'est-à-dire le temps séparant deux ondes R sur l'électrocardiogramme, en s.
- t éject., le temps d'éjection, mesuré entre le début de la systole, marqué par le début de la variation rapide d'impédance, et le début du deuxième bruit. en s.
- t ΔZ, le temps séparant le début de la systole du maximum de variation d'impédance, en s.
- Zo, ΔZ, dZ/dt sont donnés en Ω/cm ou Ω/cm.s., de manière à pouvoir comparer les résultats lorsque la distance inter-électrodes L varie.

Pour 52 sujets sur 91, L a été maintenue fixe à 3,6 cm.

Pour chaque sujet ont été notés, en outre :

- ses caractéristiques biométriques : âge, poids, taille, surface corporelle,
- les pressions artérielles systolique et diastolique.

4 - INFLUENCE DE L'AGE SUR LES VARIATIONS D'IMPEDANCE ELECTRIQUE THORACIQUE

4.1 - Résultats

. Pression artérielle

Le tableau 1 donne la moyenne générale et les moyennes pour chaque groupe d'âge.

Il n'existe aucune influence de l'âge sur la T.A. chez nos sujets, à une exception, celle du sujet le plus âgé. Ce dernier, qui a 64 ans, a une T.A. à 17/10, nettement plus élevée que la moyenne générale qui est de $12,7 \pm 0,10/7,2 \pm 0,06$ cm Hg.

. Fréquence et période cardiaques

D'après les résultats consignés dans le tableau 1 on peut voir que les sujets les plus jeunes ont une fréquence cardiaque plus élevée que les autres. Il est possible que ce phénomène puisse s'expliquer par l'appréhension d'un examen qui conditionnait l'avenir de ces jeunes gens.

La droite de régression est : $F_c = 79 - 0,25 \times (\text{âge} - 20)$

Le coefficient de corrélation $r = 0,17$ montre le peu de signification de cette relation.

. Impédance de base (Zo)

L'impédance de base est en moyenne de $0,85 \pm 0,010$ Ω/cm. Le tableau 2 montre qu'il n'existe pas de différence significative entre les différents groupes d'âge.

. Variations systoliques d'impédance (ΔZ)

Le ΔZ moyen est de $0,017 \pm 0,0005$ Ω/cm. Le tableau 2 montre qu'il existe une variation de ΔZ en fonction de l'âge.

La droite de régression confirme cette influence de l'âge sur ΔZ. Son équation est :

$\Delta Z = 0,019 - 0,0002 \times (\text{âge} - 20)$

Le coefficient de corrélation est $r = 0,40$, donc significatif à $P < 0,001$.

. Dérivée de la variation d'impédance (dZ/dt)

La vitesse maximum de variation d'impédance au cours de la systole est en moyenne de 0,152 ± 0,0055 Ω/cm.s. Le tableau 2 montre que l'âge exerce aussi une influence sur ce paramètre.

La droite de régression confirme ces données. Son équation est :
$dZ/dt = 0,182 - 0,0026 \times (\text{âge} - 20)$ $\quad r = 0,49$

. Temps d'éjection (t éject.)

Le temps d'éjection est en moyenne de 0,24 ± 0,004 s., donc une valeur conforme aux données classiques.

Le tableau 111 montre qu'il existe des différences significatives entre le groupe de 20,9 ans d'âge moyen et les autres groupes. Le temps d'éjection est en fait en relation directe avec la fréquence cardiaque, et son allongement apparent avec l'âge n'est que la conséquence de l'augmentation de la fréquence cardiaque chez les sujets les plus jeunes.

La relation entre le temps d'éjection et la période cardiaque est :
t éject. = 0,120 R.R. + 14,09 avec r = 0,49

Cette équation est très proche de celle décrite par d'autres auteurs (23,27).

. Temps mis pour atteindre le sommet de ΔZ (tΔ Z).

Le sommet de ΔZ correspond à l'augmentation maximum de volume des vaisseaux sanguins thoraciques.

Pour l'ensemble des sujets le temps mis pour atteindre ce point est en moyenne de 0,19 ± 0,004 s., autrement dit le sommet de ΔZ est atteint en moyenne 0,5 s avant la fin de la systole.

Le t ΔZ varie comme le temps d'éjection, ses variations sont donc explicables par les variations de fréquence cardiaque.

Les variations inter-individuelles de ce paramètre ne semblent en corrélation avec aucun des autres phénomènes étudiés (ΔZ, dZ/dt).

4.2 - Discussion

Les résultats précédents montrent que l'âge :

- n'a pas d'influence sur l'impédance de base,
- exerce une influence indirecte sur le temps d'éjection et le temps mis pour atteindre la variation de volume maximum, par l'intermédiaire de la fréquence cardiaque,
- a une influence nette sur ΔZ et dZ/dt.

Or ΔZ est en relation avec la variation de volume et dZ/dt avec la vitesse de variation de volume.

Comme la variation de volume est fonction de la variation de pression et de la distensibilité des vaisseaux, ΔZ et dZ/dt en sont également fonction.

Si l'on considère les variations de pression artérielle humérale comme représentatives des variations de la pression dans l'aorte, l'âge n'a pas apporté chez nos sujets, de modifications importantes à ce paramètre.

Les modifications de ΔV seraient donc attribuables à des modifications de l'élastance des vaisseaux.

Cependant le débit cardiaque baissant avec l'âge, les modifications de ΔZ et de dZ/dt observées, sont explicables à la fois par la diminution du volume systolique et par la modification de l'élastance. Une valeur trop basse de ΔZ pour une pression artérielle normale peut donc être considérée comme l'indice d'une perte d'élasticité vasculaire.

5 - EVALUATION DU DEBIT CARDIAQUE

5.1 - Méthode de calcul

KUBICEK et coll. (20) ont montré qu'avec des électrodes d'injection circulaires placées à la partie supérieure du cou et à la base du thorax et des électrodes de recueil circulaires placées à la base du cou et au niveau de l'articulation sterno-xiphoïdienne, il était possible d'évaluer le débit cardiaque en utilisant la formule :

$$\dot{Q} = \frac{\rho . L^2 . (dZ/dt) . t\,ej . F_c}{Z_o . \left[Z_o - (dZ/dt) . t\,ej \right]} \qquad (1)$$

où :

L est la distance entre les électrodes de recueil, ρ, la résistivité du sang (150 Ω/cm pour les sujets sains).

DEMANGE J. et coll. (7,8) ont proposé d'utiliser aussi cette formule dans le cas des électrodes de recueil placées en regard de l'aorte ascendante. Les résultats ne sont cependant pas satisfaisants car le débit cardiaque ainsi obtenu est le plus souvent inférieur au débit cardiaque mesuré simultanément par la méthode de dilution.

Nous avons donc admis que la valeur obtenue par la formule de KUBICEK devait être corrigée, autrement dit qu'il fallait utiliser pour calculer le débit cardiaque la formule :

$$\dot{Q} = k . \frac{\rho . L^2 . (dZ/dt) . t\,ej . F_c}{Z_o . \left[Z_o - (dZ/dt) . t\,ej \right]} \qquad (2)$$

Le facteur de correction k a été tiré de mesures simultanées effectuées à l'Hôpital Lariboisière (x), à l'Hôpital Marie Lannelongue (xx) et à l'Hôpital Ambroise Paré (xxx), d'une part avec la méthode par impédance (avec la formule de Kubicek originelle (1)), d'autre part avec la méthode de dilution.

La droite de régression des 120 couples de mesures effectuées dans ces services a pour équation (voir figure 3) :

$\dot{Q}$dil. = 0,92. $\dot{Q}$ imp + 3,7 avec r = 0,58

Le facteur de correction k à appliquer au débit obtenu par la formule de KUBICEK est donc :

$$k = \frac{\dot{Q}\ dil.}{\dot{Q}\ imp.} = 0,92 + \frac{3,7}{\dot{Q}\ imp.} \qquad (3)$$

La figure 4 montre l'évolution de k en fonction du débit cardiaque obtenu avec la formule de KUBICEK non corrigée.

Pour évaluer le débit cardiaque de nos 91 sujets sains, nous avons donc dans un premier temps, calculé le débit par la formule de KUBICEK, puis, dans un deuxième temps, multiplié ce débit "non corrigé" par le facteur de correction k qui lui correspond, donné par l'équation (3).

5.2 - Résultats

Le débit cardiaque a été en moyenne de 5,6 $\pm$ 0,08 l/mn.

Le volume systolique a été en moyenne de 74,9 $\pm$ 1,42 ml (ou 1,09 $\pm$ 0,027 ml/kg).

L'index cardiaque a été en moyenne de 3,05 $\pm$ 0,050 l/mn. m^2.

Le tableau IV et la figure 5 montrent que le débit cardiaque diminue avec l'âge.

La droite de régression est : $\dot{Q}$ = 5,97 - 0,033 x (âge - 20) (l/mn) avec r = 0,47

Le débit cardiaque diminue donc de 0,55 % par année d'âge.

Pour l'index cardiaque la droite de régression est : I.C. = 3,28 - 0,020 (âge - 20) (l/mn.m^2) avec r = 0,41.

L'index cardiaque diminue donc de 20 ml/mn.m^2 par année d'âge.

Le volume systolique, exprimé en ml ou en ml/kg, a une évolution moins nette avec l'âge. Il existe bien une diminution du volume systolique à mesure que les sujets vieillissent, mais le phénomène est surtout net à partir de 25 ans, avec une évolution en sens inverse entre 20 et 25 ans, ce qui explique peut-être la faiblesse des coefficients de corrélation des droites de régression :

Volume systolique = 77,00 - 0,176 x (âge - 20) (ml)
= 1,14 - 0,004 x (âge - 20) (ml/kg)
avec respectivement : r = 0,13 et r = 0,16.

Influence de la position :

Chez les 19 sujets chez lesquels les mesures ont été effectuées en position assise et en position couchée, on note que le passage à la position couchée diminue Z_o en moyenne de 0,14 Ω/cm, augmente ΔZ de 0,007 Ω/cm et dZ/dt de 0,036 Ω/cm.s, et diminue F_c de 12,2 %.

Le passage de la position assise à la position couchée a augmenté le volume systolique de 28,6 %, et le débit cardiaque de 14,3 %.

5.3 - Discussion

Ces résultats sont en accord avec les mesures effectuées sur des sujets au repos assis par d'autres auteurs utilisant la méthode de FICK. On sait en effet que la position du corps a une influence importante sur le débit cardiaque. Le volume systolique est de 20 à 40 % plus faible qu'en position allongée.

Cette baisse du volume systolique est en partie compensée par une élévation de la fréquence cardiaque, si bien qu'en définitive, la baisse de débit cardiaque est de 19 % (avec P< 0,001) d'après les résultats de BEVEGARD (3), DONALD (9), GRANATH (12) et STENBERG (26).

Le tableau V résume les résultats obtenus par ces auteurs, d'où nous avons exclu DONALD (9) qui a fait ses mesures sur des malades. La valeur moyenne de débit que nous avons obtenue (5,6 l/mn avec un écart type de distribution de 0,7 l/mn) ne diffère pas statistiquement des valeurs mesurées par les auteurs du tableau V (5,5 $\pm$ 1,1 l/mn). La valeur légèrement plus forte chez nos sujets peut s'expliquer par leur âge moyen moins élevé (32,1 au lieu de 42 ans).

La moyenne des volumes systoliques obtenus chez nos sujets (74,9 ml avec un écart type de distribution de 13,55) est également un peu plus élevée, et la même explication peut être retenue avec, en plus, le fait que la fréquence cardiaque de nos sujets était plus basse : 76 au lieu de 81. Cette petite différence, à son tour, peut être expliquée par l'utilisation d'une méthode non sanglante.

La relation que nous avons constatée entre le débit cardiaque et l'âge est en accord avec celle qui a déjà été signalée par des auteurs classiquement cités. C'est ainsi que BRANDFONBREMER M. et coll. (5) ont relevé une régression linéaire du débit cardiaque de 1 % par année d'âge et une diminution de l'index cardiaque de 24,4 ml/mn.m^2. Nos valeurs sont un peu faibles (20 ml/mn.m^2 de diminution de l'index

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(x) Y. Bouvrain, J.J. Gros et D. Levêque.
(xx) B. Leroy-Ladurie et D. Gilbert
(xxx) J. Bourdarias.

cardiaque par année d'âge et 0,55 % par année d'âge pour le débit cardiaque).

L'action du passage de la position assise à la position couchée a une influence du même ordre de grandeur sur le volume systolique, un peu plus faible sur le débit cardiaque (14,3 % au lieu de 19 %).

Enfin, on retrouve également la relation connue entre le volume systolique et la fréquence cardiaque : Volume systolique = 126,2 - 0,62 x F_c avec r = 0,73

La pléthysmographie électrique médiastinale haute a donc permis, après calibration de la méthode par mesure simultanée du débit cardiaque par dilution, d'obtenir des résultats satisfaisants sur des sujets sains et au repos, et ceci malgré la corrélation médiocre des mesures simultanées effectuées chez les cardiaques. Les auteurs ayant utilisé la méthode de KUBICEK chez les cardiaques ont aussi noté souvent une dispersion considérable des résultats, nettement plus importante que chez les sujets sains. En effet, le coefficient de corrélation variait de 0,83 à 0,56 chez le sujet sain et de 0,84 à 0 chez les cardiaques, ainsi qu'on peut le voir sur le tableau VI qui regroupe les résultats acquis sur l'homme sain, le cardiaque et l'animal, par différents auteurs ayant utilisé la méthode de KUBICEK originelle.

En ce qui concerne la pléthysmographie médiastinale haute, même si l'on peut démontrer que l'on mesure principalement les variations de volume de l'aorte, les relations entre celles-ci et le volume d'éjection ne sont ni simples, ni constantes. En particulier interviennent les variations de la pression et de la compliance aortiques d'un sujet à l'autre et chez un même sujet.

Il est donc nécessaire de rechercher des caractéristiques du tracé de variations d'impédance, et certaines caractéristiques biométriques, qui permettent de connaître le coefficient de correction à appliquer chez un sujet donné. On éviterait ainsi les erreurs que l'utilisation d'un coefficient empirique statistique peut amener à commettre dans certaines conditions pathologiques ou physiologiques.

6 - CONCLUSIONS

L'âge exerce une influence manifeste sur les variations de l'impédance électrique mesurée au niveau d'électrodes placées devant l'aorte ascendante. Une analyse simplifiée des résultats montre que chez des sujets sains, ces modifications de ΔZ sont en partie rattachées à des variations de la distensibilité vasculaire provoquées par l'âge.

En ce qui concerne l'évaluation du débit cardiaque, il a été nécessaire de calibrer la méthode à partir des résultats de 120 mesures simultanées du débit cardiaque par la méthode de dilution et par impédance électrique, pour aboutir à un facteur de correction de la formule de KUBICEK.

Les valeurs obtenues sur les sujets sains sont en bon accord avec celles obtenues par des auteurs ayant utilisé la méthode de FICK, en particulier en ce qui concerne l'action de l'âge et de la position. La corrélation médiocre entre les méthodes de dilution et d'impédance électrique médiastinale haute chez les cardiaques rend cette méthode pour le moment difficilement utilisable en clinique.

Cependant la facilité de mise en oeuvre, la possibilité de suivre pendant de longues durées l'évolution du débit cardiaque et du volume systolique, les renseignements donnés sur la chronologie des événements cardiaques, rendent cette méthode utile en physiologie aérospatiale.

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TABLEAU I

Nombre de sujets	Age moyen	Pression artérielle (cm Hg) Maxima		Minima		Fréquence cardiaque (mn^{-1})		Période cardiaque (RR - s)	
		Moyenne	$\bar{\sigma}$ (1)	Moyenne	$\bar{\sigma}$	Moyenne	$\bar{\sigma}$	Moyenne	$\bar{\sigma}$
19	20,9	12,7	0,19	7,2	0,11	86,5	3,59	0,71	0,026
20	25,7	12,7	0,21	7,3	0,14	70,8	2,98	0,87	0,029
19	30,5	12,6	0,18	7,2	0,13	78,6	3,07	0,79	0,029
17	37,5	12,5	0,13	7,0	0,00	70,0	2,94	0,88	0,037
15	48,4	12,6	0,20	7,1	0,14	73,1	3,18	0,86	0,039
Total : 91 (2)	32,1	12,7	0,10	7,2	0,06	76,2	1,54	0,81	0,015

(1) $\bar{\sigma}$: écart type de la moyenne.
(2) dont le sujet de 64 ans, non inclus dans les groupes par tranche d'âge et pour lequel les chiffres étaient les suivants :
T.A. : 17/10 F.C. : 97 R.R. : 0,62

TABLEAU II

Nombre de sujets	Age moyen	Zo (Ω /cm)		Δ Z (Ω /cm)		$\frac{dZ}{dt}$ (Ω /cm.s.)		$(\frac{dZ}{dt})$ x t éject.(Ω /cm)	
		Moyenne	$\bar{\sigma}$	Moyenne	$\bar{\sigma}$	Moyenne	$\bar{\sigma}$	Moyenne	$\bar{\sigma}$
19	20,9	0,87	0,018	0,020	0,0013	0,204	0,0126	0,045	0,0010
20	25,7	0,81	0,026	0,018	0,0010	0,156	0,0099	0,039	0,0027
19	30,5	0,86	0,019	0,015	0,0008	0,145	0,0088	0,034	0,0024
17	37,5	0,84	0,022	0,016	0,0010	0,131	0,0092	0,032	0,0024
15	48,4	0,85	0,029	0,014	0,0018	0,114	0,0109	0,029	0,0030
Total : 91 (1)	32,1	0,85	0,010	0,017	0,0005	0,152	0,0055	0,036	0,0013

(1) Pour le sujet de 64 ans les résultats étaient les suivants :
Zo = 0,89 Ω/cm ΔZ = 0,011 Ω/cm dZ/dt = 0,107 Ω/cms (dz/dt) x t éject. = 0,024 Ω/cm.

TABLEAU III

Nombre de sujets	Age moyen	Temps d'éjection (s)		Temps pour atteindre Δ Z (s)	
		Moyenne	σ	Moyenne	σ
19	20,9	0,22	0,006	0,17	0,007
20	25,7	0,25	0,006	0,20	0,007
19	30,5	0,24	0,006	0,18	0,010
17	37,5	0,24	0,005	0,20	0,009
15	48,4	0,26	0,016	0,20	0,014
Total 91 (1)	32,1	0,24	0,004	0,19	0,004

(1) Pour le sujet de 64 ans les résultats étaient les suivants :
t éject. = 0,22 s t Δ Z = 0,16 s.

TABLEAU IV

Nombre de sujets	Age moyen	Volume systolique moyen ml		Volume systolique moyen ml/kg		Débit cardiaque 1/mn		Index cardiaque 1/mn.m^2	
		Moyenne	σ	Moyenne	σ	Moyenne	σ	Moyenne	σ
19	20,9	73,1	2,54	1,12	0,053	6,2	0,18	3,45	0,095
20	25,7	83,0	3,22	1,21	0,063	5,7	0,13	3,15	0,119
19	30,5	69,6	2,10	0,99	0,041	5,4	0,13	2,90	0,071
17	37,5	76,6	3,29	1,09	0,058	5,3	0,14	2,85	0,088
15	48,4	72,2	4,02	1,06	0,077	5,1	0,16	2,81	0,124
Total : 91 (1)	32,1	74,9	1,42	1,09	0,027	5,6	0,08	3,05	0,050

(1) Y compris le sujet de 64 ans, non inclus dans les groupes par tranches d'âge et pour lequel les résultats étaient les suivants :

- volume systolique : 53,4 ml (0,77 ml/kg)
- débit cardiaque : 5,2 1/mn
- index cardiaque : 2,85 1/mn.m^2

TABLEAU V

AUTEUR	Nombre de sujets	Age moyen	Fréquence cardiaque mn	Volume systolique ml	Débit cardiaque m/mn
GRANATH	9	23,3	84	68	5,7
GRANATH	10	70,5	79	66	5,2
STENBERG *	8	24,8	76	68	4,8
BEVEGARD	6	24,0	82	76	6,2
BEVEGARD	9	26,3	84	70	5,9
Total...	42	44,3	81	69,1	5,5

* Débit cardiaque mesuré par la méthode de FICK indirecte, les autres auteurs ont utilisé la méthode FICK directe.

TABLEAU VI

	AUTEURS	METHODE DE REFERENCE	NOMBRE DE COUPLES DE MESURE	NOMBRE DE SUJETS	COEFFICIENT DE CORRELATION	OBSERVATIONS OU EQUATION DE LA DROITE DE REGRESSION
Sujets humains sains	KUBICEK	Dil. Col.	115	10		63 % des résultats ne s'écartent pas de plus de 20 % de la ligne d'identité.
	HARLEY	Dil. Col.	26	13	0,68	y = 0,86 X + 2,9 l/mn
	JUDY	Dil. isot.	28	17	0,58	y = 0,80 X + 4,3 l/mn
	MARTIN	Dil. col.	77	7	0,56	y = 0,70 X + 42,1 ml (vol.syst)
	SMITH	Dil. col.	35	8	0,83	y = 0,71 X + 2,1 l/mn
	BAKER	Dil. col.	21	10	0,66	y = 0,96 X + 0,6 l/mn
Sujets humains cardiaques	HARLEY	Dil. col.	26	24	0,26	Régression non donnée
	STEIGBIGEL	Dil. Col.	70	11	0,58	y = 0,62 X + 2,7
	HEATHER	Dil. Col.	38	38	0	Dispersion considérable
	KINNEN	Dil. Col.	67	67	0,84	92 % des résultats ne s'écartent pas de plus de 20 % de le ligne d'identité.
Chiens	JUDY	électro.magnét.	214	11	0,92	y = 0,91 X + 0,213 l/mn
	MARTIN	électro.magnét.	136	6	0,25	y = 0,24 X + 10,7 ml (vol.syst)
	WITSOE	électro.magnét.	305	14		30 % des résultats s'écartent de plus de 20 %.

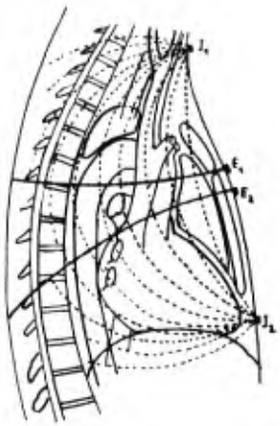


FIGURE 1 - Coupe schématique du thorax humain.
I1 et I2 : électrodes d'injection
E1 et E2 : électrodes de recueil

Les lignes de courant (en pointillé) et les surfaces équipotentielles (en trait plein) représentées sont celles qui existeraient dans un milieu de résistivité électrique homogène. Dans la réalité elles ne présentent pas cette régularité.

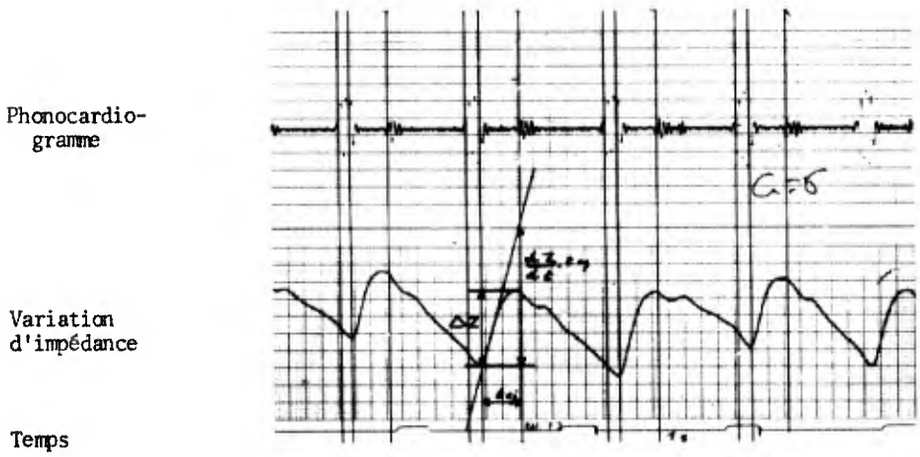


FIGURE 2 - Exemple d'enregistrement de variation d'impédance électrique médiastinale haute.

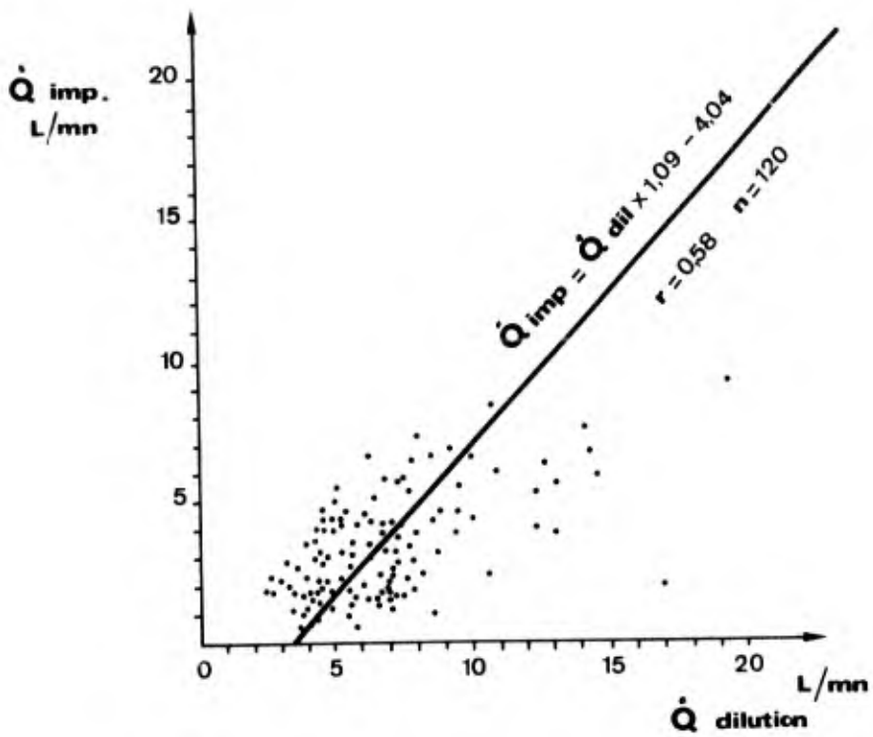


FIGURE 3 - Résultats des mesures simultanées du débit cardiaque par impédance électrique (en utilisant la formule de KUBICEK) et par dilution de colorant, effectuées sur des cardiaques.

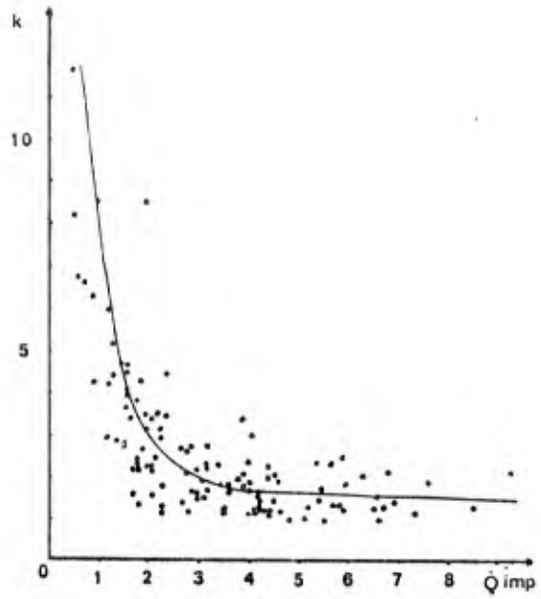


FIGURE 4 - Evolution du coefficient de correction (k) de la formule de KUBICEK en fonction du débit cardiaque mesuré par impédance (Q imp) sans correction.

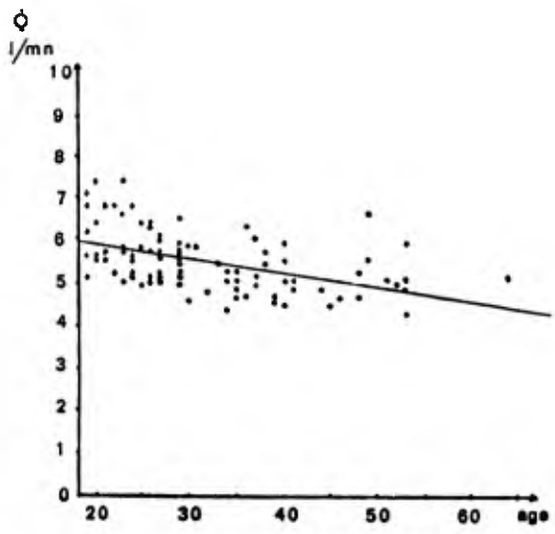


FIGURE 5 - Evolution du débit cardiaque, mesuré par la méthode d'impédance électrique, en fonction de l'âge.

THE INFLUENCE OF ALCOHOL ON SOME VESTIBULAR TESTS.

A.J.GREVEN AND W.J.OOSTERVELD
WILHELMINA GASTHUIS
UNIVERSITY OF AMSTERDAM
AMSTERDAM , THE NETHERLANDS.

The influence of alcohol on the vestibular system is a well known fact. Flourens (1842) was the first to report a nystagmus after the intake of alcohol. Since 1911 (Bárány) several authors described the effect of alcohol on vestibular tests.

In human subjects we studied the influence of an alcoholic beverage on some vestibular tests ; 48 experiments were conducted in 27 normal humans , 15 men and 12 women. The effect of alcohol was observed upon fixation nystagmus , gaze nystagmus , the visual tracking pendulum test , and the optokinetic induced nystagmus. Alcohol was given in four different quantities : 0.1 , 0.2 , 0.4 and 0.8 g/kg body weight,as whisky (34°). With each dosage 12 experiments were performed in 12 subjects (6 men and 6 women).

RESULTS :

Fixation nystagmus.
This nystagmus is found when the subject fixates a target situated straight in front of him at a distance of more than 1 m. The direction of the slow phase of fixation nystagmus can be towards either side , the speed is usually not more than 5^{o}/s , the frequency not more than 1 beat per second. A fixation nystagmus appears when there is a disturbance in the pathways of the position correcting loop for visual tracking which keeps the eyes on target. The presence of fixation nystagmus indicates among others oculo-motor disorders.
In 48 experiments the subjects had to fixate a red light at a distance of 3 m. Recordings of eye movements were made before and at various intervals after the intake of alcohol (33 , 63 , 93 , 153 , 273 and 393 minutes).
In none of the subjects a fixation nystagmus was found. Blood alcohol determinations were made , which varied from 0 to 1.0 °/oo. So we did not find fixation nystagmus in humans after the intake of 0.1-0.8 g/kg body weight in any of the subjects.

"Gaze" deviation nystagmus.
This nystagmus is caused by a disturbance of the voluntary gaze system.The testing is done with a deviation of the eyes of 20^{o} and 40^{o} in the horizontal plane. A gaze deviation nystagmus is always a pathological finding and indicates central lesions , located in the area between medulla oblongata , cerebellum and mesodiencephalon. However , intoxications with barbiturates and increased intracranial pressure can also be a cause of this nystagmus.
The subjects were exposed to the test before and after the intake of alcohol. The tests were done at 34 , 64 , 94 , 154 , 274 and 394 minutes after the intake. A display of the results is given in table 1.
After the intake of a dosage of 0.1 g alcohol/kg body weight in two out of 12 subjects a "gaze"nystagmus was recorded. The frequency was less than 1 beat per second.
After the intake of a dosage of 0.2 g alcohol/kg body weight in five out of 12 subjects a "gaze"nystagmus was found , however , in three of them in one direction only. The frequency was less than 1 beat per second.After the intake of 0.4 g alcohol /kg body weight in four subjects out of 12 a "gaze"nystagmus was found , in two of them in one direction only ; the frequency was very low (less than 1 beat per second).
After the highest used dosage of alcohol : 0.8 g/kg body weight , one subject out of 12 showed gaze nystagmus in all 4 tests , with a frequency of more than 1 beat per second. Another person had nystagmus in all four gaze directions with a lower frequency than 1 beat per second. A third person had gaze nystagmus only in one direction at one examination.
Our conclusion is that gaze nystagmus is a rare finding in subjects after the intake of 0.8 g alcohol/kg body weight. In none of the subjects gaze nystagmus was found that could be detected by an observer without the aid of the electronystagmography , since the speed of the nystagmus was much too small.

Pendulum visual trackingtest.
The movements of the eye when tracking a moving target are smooth and without irregularities. When a target oscillates in front of a normal subject , the recorded eye movements show a smooth sinusoidal line.
The tracking test was conducted in 27 subjects in 48 experiments , before and after the intake of alcohol (at 38 , 68 , 98 , 158 , 278 and 398 minutes).The subject kept his head immobilized and looked successively with both eyes together and with each eye seperately. Each investigation lasted 60 seconds. The target was moving at a distance of 2.5 m , in such a way that the angle of the gaze of the subject with his median plane was 20^{o} to the left and to the right. The oscillation time was 2.2 seconds.
We called one saccade/4 sinusoidal movements a very slightly disturbed performance , one saccade/one sinusoidal movement a slightly disturbed performance , 2 saccades/one sinusoidal movement moderately disturbed performance and 3 or more saccades/one sinusoidal movement a strongly disturbed performance.
Subjects who have drunk the lower quantities of alcohol (0.1 and 0.2 g/kg body weight) showed a difference in the results found when they looked either with both eyes or with one eye only. This difference is less pronounced in the subjects who has drunk the higher quantities of alcohol (0.4 and 0.8 g/kg body weight).
The results show a big individual difference : some subjects show no effect at all after any dosage of alcohol , others have a strongly disturbed performance after only 0.1 g alcohol/kg body weight. None of the subjects had any awareness of the quality of his performance.
The results are given in table 2-5.In three out of 12 subjects after a quantity of 0.1 g alcohol/kg body weight of the subject either no effect or a very slight one was seen ; three out of 12 subjects showed a slight effect , three a moderate and three a strong effect.
In three out of 12 subjects a dosage of 0.2 g alcohol/kg body weight of the subject had either no or a very slight effect ; a slight one was found in two out of 12 subjects , a moderate one in six and a strong effect in one out of 12 persons. In two out of 12 subjects 0.4 g alcohol/kg body weight of the subject provoked no or a very slight disturbance of the test performance. Two out of 12 subjects had a slight , six a moderate and two a strong disturbance of the smooth pursuit movement. The highest quantity : 0.8 g alcohol/kg body weight of the subject elicited no effect or a very slight one in two out of 12 subjects. In two out of 12 a slight effect and in eight a strong one was found.
There was a clear relation between the dosage of the alcohol and the appearance of saccades in the eye

movements. Between the results of the two lowest dosages only a slight difference appears.
The number of saccades has a biphasic curve in time (graphics 1-4). The lowest number of saccades was found at the test conducted 158 minutes after drinking 0.1 g alcohol/kg body weight of the subject. After drinking of 0.2 or 0.4 g alcohol/kg body weight the lowest number was found 278 minutes after drinking. No minimum was seen when the subjects had drunk 0.8 g alcohol/kg body weight. Probably this minimum is reached more than 398 minutes after the intake.

Optokinetic induced nystagmus.
Optokinetic induced nystagmus is a physiological nystagmus elicited by a rotation of the visual surrounding of the subject. Mizoi (1968) discerned 3 phases of optokinetic nystagmus : up to a velocity of 40°/s of the stimulus the subjects track the stimulus with the same speed of the eyes ; from $40\text{-}100^{\circ}$/s the speed of the eye movements increase more slowly than the speed of the stimulus ,the maximum speed of the eyes is about 60°/s ; if a stimulus with a speed of more than 100°/s is applied , the speed of the eye movements show s a relative decrease.
In 48 experiments carried out in 27 subjects the influence of alcohol on optokinetic nystagmus was studied. Tests were conducted before the drinking of alcohol and 43 , 73 , 103 , 173 , 283 and 403 minutes after the drinking. The subject had to keep his head immobilized and was asked to fixate black and white stripes , 6 cm wide moving at a distance of 70 cm from the subject. Recordings were made during periods of 15 seconds for each stimulus. The velocity of the optokinetic stimulus was 20 , 40 , 60 , 80 , 100 and 120°/s. The tests were done both in clockwise and in counterclockwise direction.
A display of the results is shown in table 6-9. At an interval of 43 minutes after the drinking of 0.1 g alcohol/kg body weight of the subject in 12 subjects the mean speed of the slow phase of optokinetic nystagmus for all 12 stimuli was lower than 100% of the speed before drinking.After 73 minutes this was seen for 10 of the 12 stimuli, 103 minutes after the drinking for all 12 stimuli, after 163 minutes for 9 out of 12 stimuli, after 283 minutes for 5 and after 403 minutes for 9 out of 12 stimuli.
If 0.2 g alcohol/kg body weight was drunken by 12 subjects , only 2 out of 12 stimuli provoked a mean speed of the slow phase of optokinetic nystagmus higher than 100% at the point of time 73 minutes after the drinking , 283 and 403 minutes after the drinking this was found for respectively one and 4 stimuli. The mean speed of the slow phase was always less than 100% in the group subjects who drunk 0.4 and 0.8 g alcohol/kg body weight. The suppression was stronger shortly after the intake.
The frequency of optokinetic nystagmus was not influenced by drinking alcohol.
As found also in the pendulum results , the subjects were not aware that their performance was less good after the intake of alcohol.

CONCLUSION :

Our conclusion is that alcohol administered in quantities of 0.1-0.8 g/kg body weight of the subject influence the performance of pendulum tests and the optokinetic nystagmus. An alcoholgazenystagmus is a very rare finding and a fixation nystagmus was never found.

time: (minutes)	before drinking	after drinking 34	64	94	154	274	394
subject nr 5							
gaze							
20° left	-	L $1^{\circ}\text{-}2^{\circ}$/0,7	L $1^{\circ}\text{-}2^{\circ}$/0,9	L $2^{\circ}\text{-}3^{\circ}$/0,8	-	-	-
40° left	-	L $2^{\circ}\text{-}4^{\circ}$/1,2	L $2^{\circ}\text{-}3^{\circ}$/0,9	L $1^{\circ}\text{-}3^{\circ}$/0,7	-	-	-
20° right	-	R 3° /2,4	R 1° /0,9	R 2° /0,6	-	-	-
40° right	-	R $3^{\circ}\text{-}4^{\circ}$/1,9	R 3° /2,1	R $2^{\circ}\text{-}3^{\circ}$/0,7	-	-	-
subject nr 19							
gaze							
20° left	-	-	-	-	-	-	-
40° left	-	-	-	-	-	-	-
20° right	-	-	-	-	-	-	-
40° right	-	R $5^{\circ}\text{-}11^{\circ}$/1,4	-	-	-	-	-

"Gaze"nystagmus found after drinking of 0,8 g alcohol/kg body weight of the subject.

direction of the slow phase of nystagmus, speed of the slow phase of nystagmus/frequency of "gaze"nystagmus.
L= nystagmus to the left.
R= nystagmus to the right.

table 1

table 2

time: (minutes) / subjects	before drinking	after drinking 38	68	98	158	278	398
2	1/1/1	1/1/1	1/3/4	3/4/3	2/1/3	3/3/3	3/3/4
1	0/0/0	0/1/1	2/1/0	0/0/0	0/0/0	0/0/0	0/0/0
5	0/0/1	0/1/1	2/3/3	1/2/3	3/3/3	1/2/2	1/1/1
16	0/0/0	0/0/1	1/1/1	0/0/1	0/1/1	0/0/1	0/0/1
15	0/0/0	1/1/1	2/2/2	2/2/2	0/2/2	1/2/2	1/2/2
3	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	1/1/0	0/0/0
8	0/0/0	1/4/3	2/3/3	3/3/3	0/1/2	1/2/1	0/0/2
4	0/0/0	2/3/3	3/4/4	3/4/4	2/2/2	3/3/3	3/2/3
21	0/0/0	0/0/0	2/2/2	0/0/0	0/0/0	0/0/0	1/1/1
22	0/0/0	5/5/5	0/3/4	4/4/4	0/3/3	2/3/2	0/0/2
18	0/0/0	1/1/1	0/1/1	0/1/1	0/0/0	1/1/1	0/0/0
10	0/0/0	1/1/1	1/1/1	2/2/1	1/1/1	1/1/2	3/3/3
mean value	0,1/0,1/0,2	1,0/1,5/1,5	1,3/2,0/2,1	1,5/1,8/1,8	0,7/1,2/1,4	1,2/1,5/1,4	1,0/1,0/1,6

The result of the pendulum test after 0,1 g alcohol/kg body weight of the subject.

table 3

time: (minutes) / subjects	before drinking	after drinking 38	68	98	158	278	398
1	0/0/0	2/2/2	2/2/3	2/2/1	3/2/2	3/3/3	2/2/0
5	0/0/1	3/3/3	2/3/2	1/3/0	1/2/2	0/3/2	3/2/3
3	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
13	1/1/0	2/2/3	1/1/1	2/3/2	1/1/0	0/0/1	0/0/3
14	0/0/0	0/0/0	1/0/0	0/0/0	0/0/1	0/1/1	0/0/2
15	0/0/0	2/3/3	2/3/3	1/3/3	0/2/2	0/0/0	0/1/1
16	0/0/0	1/0/2	2/1/1	1/1/1	0/0/1	0/0/0	0/0/0
17	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
18	0/0/0	0/0/3	2/0/0	0/0/0	0/0/0	0/0/0	0/0/0
8	0/0/0	1/4/3	2/3/3	2/3/4	3/4/3	2/2/2	1/3/3
19	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
20	0/0/0	1/2/2	1/1/0	0/0/1	1/0/0	0/0/2	3/0/0
mean value	0,1/0,1/0,1	1,0/1,3/1,8	1,3/1,2/1,1	0,8/1,3/1,0	0,8/0,9/0,9	0,4/0,8/0,9	0,8/0,7/1,0

7

The result of the pendulum test after 0,2 g alcohol/kg body weight of the subject.

table 4

time: (minutes) / subjects	before drinking	after drinking 38	68	98	158	278	398
1	0/0/0	1/1/1	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
2	0/0/0	1/3/2	2/2/3	0/4/2	0/0/0	0/0/1	0/0/0
3	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
4	0/0/0	2/2/4	2/3/4	2/2/2	2/4/4	0/1/1	0/0/1
5	0/0/1	2/3/3	1/2/2	2/3/2	0/0/0	1/0/1	2/2/1
6	0/0/0	0/0/0	0/0/2	0/0/1	1/0/0	0/2/2	0/0/0
7	0/0/0	0/0/0	0/0/2	0/3/3	0/2/0	0/0/0	0/2/2
8	0/0/0	3/2/2	3/3/3	3/3/3	0/2/2	1/1/1	3/3/3
9	1/1/1	3/2/2	3/3/2	1/1/2	3/0/1	1/1/0	2/2/2
10	1/1/1	2/3/1	2/2/1	2/0/2	2/1/2	0/1/0	2/1/2
11	0/1/0	1/0/1	2/2 ?	3/3/3	3/3/3	2/2/2	3/2/1
12	0/0/0	1/1/1	2/1/1	2/0/1	0/0/0	0/0/1	0/1/1
mean value	0,2/0,3/0,3	1,3/1,4/1,4	1,4/1,5/1,8	1,3/1,5/1,8	0,9/1,0/1,0	0,4/0,7/0,8	1,1/1,2/1,2

The result of the pendulum test after 0,4 g alcohol/kg body weight of the subject.

results of the pendulum test fixating with both eyes/ with only the left eye/ with only the right eye.
0= no saccades
1= one saccade / 4 sinusoidal eyemovements
2= one saccade / one sinusoidal eyemovement
3= 2 saccades / one sinusoidal eyemovement
4= 3 or more saccades / one sinusoidal eyemovement

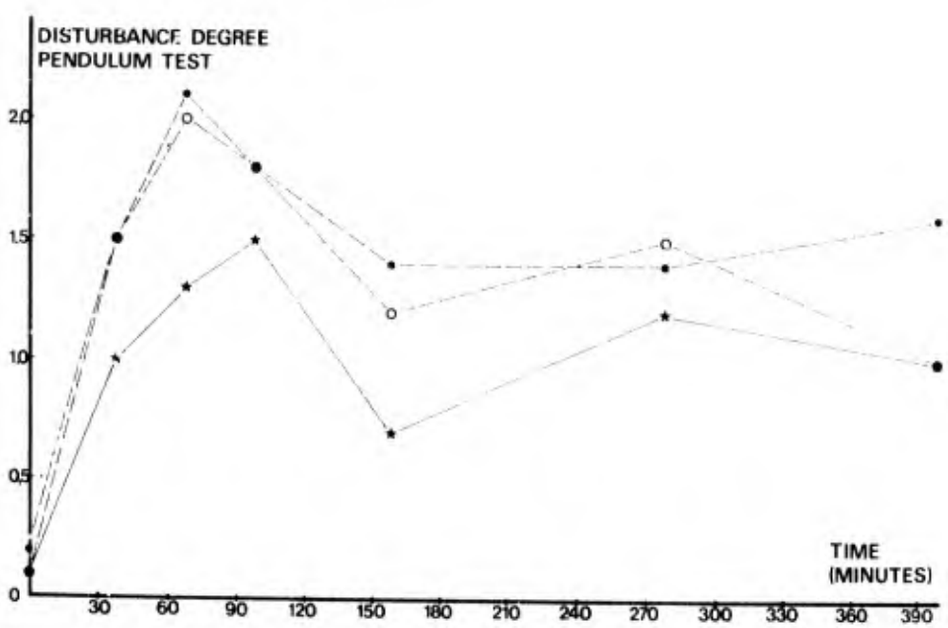
table **5**

time: (minutes) / subjects	before drinking	after drinking 38	68	98	158	278	398
5	0/0/1	4/4/4	4/4/4	4/4/4	3/4/4	2/3/3	0/3/2
20	0/0/0	0/0/0	0/0/0	0/0/0	0/0/1	0/0/0	0/0/0
3	0/0/0	1/1/1	0/1/1	1/0/0	0/0/0	0/0/0	0/0/0
1	0/0/0	4/4/4	3/4/4	3/3/3	2/3/3	1/1/1	0/1/0
23	0/1/1	2/2/2	4/4/3	3/3/3	0/1/0	2/0/1	1/0/0
8	0/0/0	3/3/3	1/4/4	2/4/4	4/4/4	1/2/4	1/1/2
24	0/0/0	2/1/0	1/0/1	1/1/1	1/0/0	0/0/1	0/0/2
10	1/1/1	2/4/3	4/3/4	4/4/4	4/4/4	2/3/2	2/2/2
25	0/1/1	3/4/4	4/4/4	4/4/4	3/3/4	2/3/3	3/2/2
26	0/0/0	0/0/0	1/2/2	2/2/0	0/0/0	0/1/0	0/0/0
27	0/0/0	2/2/2	3/3/3	4/4/4	3/3/2	1/1/0	0/0/0
19	0/0/0	4/4/4	3/4/2	2/2/3	1/1/1	0/2/2	1/0/0
mean value	0,1/0,3/0,3	2,3/2,4/2,3	2,6/2,8/2,7	2,5/2,6/2,5	1,8/1,9/1,9	0,9/1,3/1,4	0,7/0,8/0,8

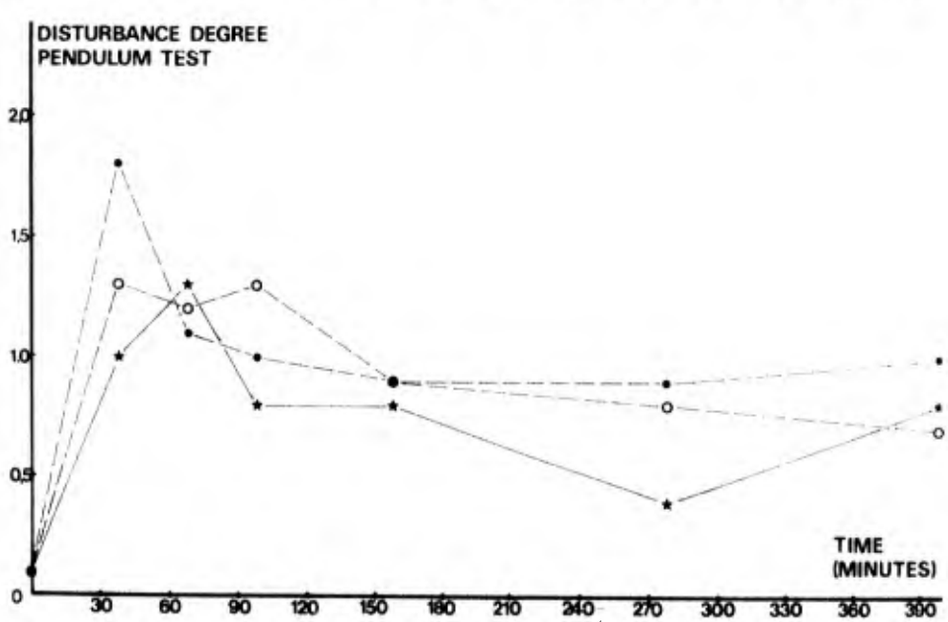
The result of the pendulum test after 0,8 g alcohol/kg body weight of the subject.

results of the pendulum test fixating with both eyes/ with only the left eye/ with only the right eye.
0= no saccades
1= one saccade / 4 sinusoidal eyemovements
2= one saccade / one sinusoidal eyemovement
3= 2 saccades / one sinusoidal eyemovement
4= 3 or more saccades / one sinusoidal eyemovement

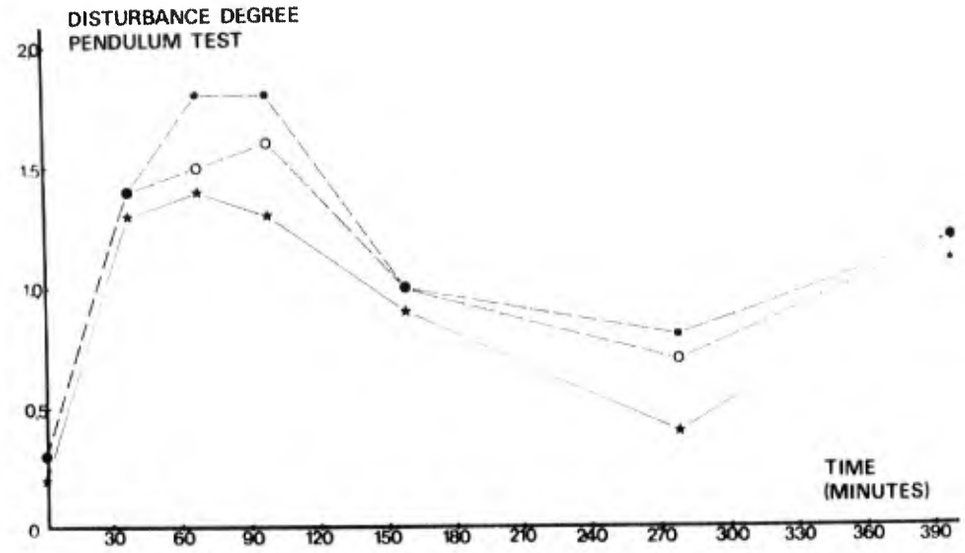
graphic **1**



graphic **2**



graphic **3**



graphic **4**

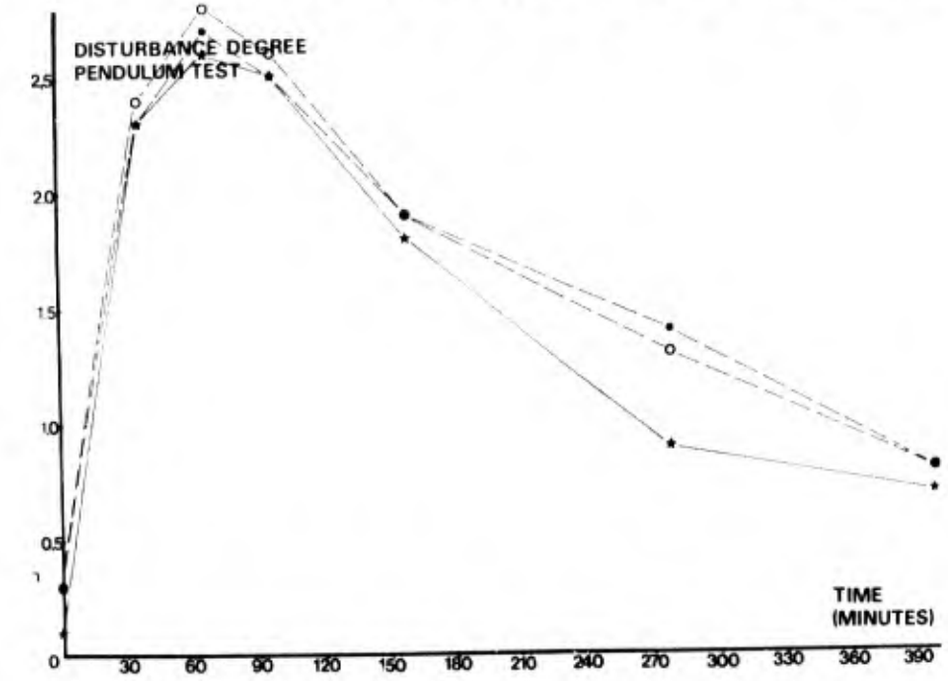


table **6**

time:	before drinking	after drinking					
(minutes)		43	73	103	163	283	403
stimulus							
H 20°/s	100	84	90	86	94	111	99
AH 20°/s	100	92	97	89	93	107	94
H 40°/s	100	101	96	96	105	108	101
AH 40°/s	100	89	92	87	100	108	100
H 60°/s	100	97	106	95	97	110	94
AH 60°/s	100	76	91	86	94	86	90
H 80°/s	100	97	99	85	98	95	90
AH 80°/s	100	94	101	95	100	100	102
H 100°/s	100	87	96	86	112	94	102
AH 100°/s	100	92	96	88	99	95	96
H 120°/s	100	82	81	81	87	88	96
AH 120°/s	100	94	92	82	91	91	96

The mean speed of the slow phase of optokinetic nystagmus after drinking of 0,1 g alcohol/kg body weight of the subject, as percentage of this speed before drinking.

table 7

time:	before drinking	after drinking					
(minutes)		43	73	103	163	283	403
stimulus							
H 20°/s	100	92	89	79	89	91	88
AH 20°/s	100	83	80	78	85	88	89
H 40°/s	100	94	95	90	95	99	96
AH 40°/s	100	91	90	88	92	86	92
H 60°/s	100	93	107	86	95	92	96
AH 60°/s	100	89	98	88	92	100	98
H 80°/s	100	87	99	93	93	97	93
AH 80°/s	100	96	100	94	99	98	103
H 100°/s	100	87	91	84	86	97	96
AH 100°/s	100	81	95	87	91	90	101
H 120°/s	100	91	88	87	90	100	101
AH 120°/s	100	94	92	87	93	93	104

The mean speed of the slow phase of optokinetic nystagmus after drinking of 0,2 g alcohol/kg body weight of the subject, as percentage of this speed before drinking.

table 8

time:	before drinking	after drinking					
(minutes)		43	73	103	163	283	403
stimulus							
H 20°/s	100	85	86	90	84	95	95
AH 20°/s	100	87	95	96	93	107	105
H 40°/s	100	85	95	97	86	110	112
AH 40°/s	100	80	91	92	96	104	108
H 60°/s	100	81	88	93	94	102	110
AH 60°/s	100	67	72	75	80	87	92
H 80°/s	100	66	77	81	88	99	102
AH 80°/s	100	62	63	80	84	105	105
H 100°/s	100	70	74	83	91	106	103
AH 100°/s	100	59	72	75	91	90	115
H 120°/s	100	67	81	84	87	96	105
AH 120°/s	100	54	62	70	78	99	93

The mean speed of the slow phase of optokinetic nystagmus after drinking of 0,4 g alcohol/kg body weight of the subject, as percentage of this speed before drinking.

table 9

time:	before drinking	after drinking					
(minutes)		43	73	103	163	283	403
stimulus							
H 20°/s	100	66	71	76	78	88	91
AH 20°/s	100	65	69	73	82	97	90
H 40°/s	100	56	64	69	79	88	94
AH 40°/s	100	57	72	83	93	102	114
H 60°/s	100	61	70	80	97	105	115
AH 60°/s	100	43	52	59	74	88	93
H 80°/s	100	56	60	68	82	98	107
AH 80°/s	100	55	68	69	84	102	120
H 100°/s	100	58	66	68	90	114	111
AH 100°/s	100	57	64	67	74	107	110
H 120°/s	100	67	68	74	84	117	106
AH 120°/s	100	68	59	71	91	115	125

The mean speed of the slow phase of optokinetic nystagmus after drinking of 0,8 g alcohol/kg body weight of the subject, as percentage of this speed before drinking.

Apport de la biopsie cutané dans le dépistage de la sénescence vasculaire, relations avec le carotidogramme. (The contribution of skin biopsy to the detection of vascular senescence - Relationship with carotigram).

par C.F. NOGUES - R. CARRE - F. LIZERAY - E. CAVA.

Résumé.

La surveillance médicale du personnel navigant au cours des examens révisionnels est axée sur le dépistage des affections dégénératives cardiovasculaires, en plus il paraît séduisant d'apprécier l'âge biologique des pilotes.

Nous avons montré l'intérêt du rapport I/A du carotidogramme (I étant amplitude de l'incisure catacrote, A amplitude totale du tracé). L'étude effectuée sur modèle hydraulique montrait que ce rapport I/A augmentait avec les résistances périphériques et la diminution de l'élasticité.

Chez 93 membres du personnel navigant, nous avons comparé ce rapport avec les altérations cutanées constatées à la biopsie de peau faite au niveau de l'épine iliaque postérieure ; ces biopsies de peau étant typées suivant les critères du Professeur BOUISSOU.

Il existe une relation très significative entre le type de peau et le rapport I/A (probabilité est de 13/10000).

Ce travail montre donc que le carotidogramme s'avère un moyen d'exploration de la pulsabilité artérielle et permet une approche de l'âge biologique.

La surveillance médicale du Personnel Navigant au cours des examens révisionnels est axée sur le dépistage des affections dégénératives cardiovasculaires. L'intégrité anatomique et fonctionnelle du coeur et des vaisseaux est en effet nécessaire à la mise en jeu de régulation adaptées aux phases du vol.

Au cours de ces examens, le vieillissement artériel et la surcharge athéroscléreuse des vaisseaux peuvent être appréciés par les examens clinique et paracliniques. Parmi les moyens mis en oeuvre, les examens mécanographiques, et tout particulièrement le carotidogramme, sont utilisés largement par les médecins experts.

Une étude conjointe des enregistrements mécanographiques de la pulsation artérielle et du vieillissement cutané a été conduite par le Centre Principal d'Expertise du Personnel Navigant et le laboratoire de Biologie Cellulaire du Centre de Recherches de Médecine Aéronautique.

I - Le carotidogramme.

La courbe enregistrée présente l'allure générale suivante :

- elle s'élève rapidement (10 à 12 centièmes de seconde après le début des ondes QRS de l'ECG) pour dessiner un pic suivi d'un plateau ou d'un sommet plus ou moins émoussé,
- puis elle amorce une descente pour arriver à l'incisure catacrote, reflet propagé au début de la diastole. La courbe revient à la ligne de base après avoir dessiné une onde positive dicrote, plus ou moins accentuée.

Ces accidents seraient la résultante de plusieurs facteurs :

- l'onde principale jusqu'à l'incisure catacrote représente la phase d'expulsion ventriculaire gauche dans un réseau artériel de résonance où les résistances périphériques vont modifier le régime oscillatoire.

- l'onde dicrote naît, pour certains, au voisinage du diaphragme ; pour d'autres, elle est le résultat d'une rétraction aortique. Elle est étroitement liée à la fermeture sigmoïdienne car elle disparaît dans l'insuffisance aortique sévère. (10). Cette onde dicrote est également modifiée par les résistances périphériques dont l'augmentation dans l'hypertension s'accompagne d'une ascension de l'onde le long de la pente descendante du piézogramme.

Expérimentalement, sur un modèle hydraulique, on peut à débit constant faire varier l'élasticité d'un système artériel pulsatile ainsi que les résistances périphériques. Un enregistrement pléthysmographique montre une courbe de morphologie semblable à celle du piézogramme. Sur un tel modèle, l'ascension de l'onde dicrote sur le versant descendant est obtenu en supprimant l'effet windkessel ou en augmentant les résistances périphériques.

Dans ces conditions, le rapport I/A (hauteur d'apparition de l'incisure de l'onde dicrote sur amplitude de l'onde principale) augmente avec la diminution de l'élasticité ou l'augmentation des résistances périphériques (8).

Ces faits confirment les modifications pathologiques observées en clinique.

Pour déterminer le rôle propre des modifications de l'élasticité des artères dans la genèse de ces variations du carotidogramme, une étude histologique du tissu élastique cutané, considéré comme représentatif, a été conduite parallèlement aux enregistrements mécanographiques.

Avant d'exposer nos moyens d'études et la méthode utilisée, il convient de faire un bref rappel de quelques notions d'histologie cutanée.

II - Rappel histologique.

- Le tissu élastique sous épidermique. Le réseau élastique sous épidermique se constitue progressivement après la naissance.

. chez l'adulte, dans le derme papillaire, les fibres sont graciles et ascendantes venant du derme sous papillaire, elles atteignent la membrane basale de l'épiderme par de fines arborescences Au niveau du derme sous papillaire, les fibres sont épaisses, parallèles à la surface de la peau, tandis que dans le derme profond et moyen, le réseau élastique revêt une architecture plexiforme. Autour de ce réseau élastique, le tissu collagène est représenté par des trousseaux épais légèrement moins denses dans la zone papillaire.

. chez le vieillard, le réseau élastique papillaire est raréfié, les fibres sont irrégulières, fragmentées et n'atteignent plus l'épiderme.

- dans sa classification des types lésionnels cutanée, BOUISSOU (1) distingue à partir d'une structure normale de l'adulte ou peau de type O, une peau de type I où il existe une zone "désertique" localisée entre l'épiderme et le derme sous papillaire ; le tissu élastique y a pratiquement disparu et ne persistent que quelques fibrilles ascendantes frêles et mal colorées rejoignant la basale épidermique. Le tissu collagène est homogène, les fibres sont désorientées, amincies et fragmentées.

Une peau de type II. La zone désertique est continue sur toute la longueur du derme papillaire, son épaisseur est au moins égale à celle de l'épiderme adulte non atrophique.

Les fibres collagènes y sont frêles et contrastent avec les faisceaux denses du derme sous papillaire.

Une peau de type III où s'exagèrent les lésions précédentes, ce type serait surtout rencontré après 65 ans.

- En microscopie électronique, outre les altérations des fibres élastiques dont la matrice se charge de grains denses apparaissent des lésions des fibroblastes (2, 4, 11).

En effet jusqu'à 25 ans environ, le fibroblaste est avant tout une cellule active et sécrétante ; peu à peu, le cytoplasme devient plus dense, des cytolysosomes apparaissent traduisant une nécrose focale de la cellule.

III - Moyens d'études et méthodes.

Cette étude a porté sur 93 sujets volontaires, membres du Personnel Navigant civil ou militaire, lors du renouvellement semestriel de l'aptitude au vol.

L'âge des sujets variait entre 20 et 52 ans.

Sur chaque sujet, au cours de l'examen médical, ont été effectués un enregistrement du mécanogramme carotidien et une biopsie cutanée.

L'appareillage utilisé est du type THOMSON TELCO, le capteur est un quartz piézo électrique à variation d'inductance. Après amplification du signal, le tracé est enregistré sur papier photographique. Sur chaque tracé, six rapports I/A ont été calculés, le chiffre retenu représentant la moyenne arithmétique de ces six mesures.

Le prélèvement cutané a été effectué au niveau de l'épine iliaque postérieure : sans anesthésie locale, la peau était incisée au ciseaux de Mayo, le fragment de peau mesurant environ 8 X4 mm était fixé dans du liquide de BOUIN-HOLLANDE et inclus en paraffine. Les étalements après section des blocs ont été colorés à l'hematoxyline de Verhoeff. L'interprétation des lames a été conduite en double aveugle.

En outre, un prélèvement destiné à l'étude des lésions cellulaires a été fixé en glutaraldéhyde tamponné pour l'observation en microscopie électronique sur Philips EM 300.

IV - Résultats.

Un des types lésionnels définis précédemment a été attribué à chaque prélèvement de peau selon la raréfaction du tissu élastique ; aucun type 3 n'a été reconnu.

L'ensemble des résultats, rapportés dans la thèse de LIZERAY (7), comprend pour chaque sujet, l'âge, la valeur du rapport I/A et le type histologique.

L'étude statistique a utilisé la méthode de l'analyse de la variance entre les stades d'atrophie élastique, l'âge et les valeurs de I/A.

Il existe une variation hautement significative entre les stades du vieillissement élastique cutané et l'âge des sujets ($P = 0,0005336$) traduisant la raréfaction, déjà connue, du tissu élastique chez le sujet âgé.

Si l'on considère les types de peau et les valeurs du rapport I/A, la variation est également hautement significative ($P = 0,0013157$). Ce fait introduit la notion d'un âge biologique puisqu'obtenu sans tenir compte de l'âge chronologique.

Ainsi, pour un sujet d'âge donné, la diminution du tissu élastique sous épidermique s'accompagne d'une élévation du rapport I/A. Ce rapport semble donc être un moyen d'approche dans l'évaluation du capital élastique de l'organisme.

En microscopie électronique, le prélèvement étudié chez un sujet de 40 ans, a permis de retrouver des altérations conjonctives cellulaires et fibrillaires.

Les fibres élastiques sont rares : elles apparaissent constituées de lames homogènes sans structure ni granulation dense ; leurs unités élémentaires, plus ou moins denses aux électrons, sont bordées d'éléments microfibrillaires.

Les faisceaux de fibres collagènes sont frêles au niveau de la zone papillaire, les fibres ont une périodicité transversale d'environ 650A°, certaines présentent

un calibre irrégulier, elles sont fréquemment associées à des éléments microfibrillaires au voisinage des cellules fibroblastiques.

Les fibroblastes. Leur activité "sécrétoire" persiste et les signes d'activité cellulaire se reconnaissent aisément : le nucléole est visible, l'appareil de Golgi bien développé, le réticulum endoplasmique bordé de ribosomes est parfois dilaté autour d'un matériel finement granuleux. Cependant, des signes de souffrance cellulaire apparaissent déjà : on observe d'assez nombreuses cellules fibroblastiques sombres, riches en corps denses lysosomiaux, les mitochondries sont altérées, leur matrice est claire parfois ponctuée de calcifications, les crêtes sont dissociées.

V - Discussion.

La sénescence s'accompagne de modifications du tissu conjonctif touchant à la fois les macromolécules intercellulaires et les cellules qui les élaborent. Le collagène, l'élastine, les glycoprotéines de structure et les protéoglycannes sont synthétisés par les fibroblastes ; selon ROBERT tout se passe comme si ces synthèses étaient programmées : protéoglycannes et glycoprotéines de structure seraient synthétisés essentiellement au cours de la vie embryonnaire, tandis que le collagène et l'élastine prendraient le relai. La production d'élastine serait réprimée très tôt au cours de la vie adulte alors que l'édification du collagène resterait plus modulée.

L'importance de l'élastine dans le tonus normal de la peau et des vaisseaux est démontrée. Avec l'âge, le capital de tissu élastique se dégrade, des lipoprotéines se déposent et les fibres élastiques se fragmentent sous l'action d'élastases. Une synthèse compensatrice de microfibrilles s'observe : elle est le point d'appel de sels calciques à l'origine des plaques d'athérome calcifiées (9).

Le vieillissement affecte également la cellule conjonctive ; les lésions cellulaires et les nécroses focales démontrées par l'étude ultrastructurale témoignent de ces phénomènes qui s'associent aux erreurs de synthèse (ORGEL) et à la chronologie de l'élaboration des macromolécules (ROBERT, 9). Par ailleurs, ce pouvoir de multiplication des cellules n'est pas illimité. On sait en effet que le taux de doublement d'une population cellulaire en culture s'abaisse lorsque l'âge du donneur augmente (5). Ces faits débouchent sur des déductions relativement pessimistes : si les progrès de la médecine, et la protection contre l'excès de radicaux libres, augmentent l'espérance de vie à la naissance, la longivité humaine en soi, demeure peu modifiée.

Notre travail met l'accent sur ce témoin du vieillissement biologique qu'est l'atrophie du tissu élastique associé aux lésions cellulaires.

Cette atrophie du tissu élastique apparaît comme un phénomène général à l'organisme puisque l'examen de la peau en un point donné est le reflet du vieillissement élastique aortique comme l'ont montré BOUISSOU et ses collaborateurs (1).

L'exploration cardiovasculaire par le carotidogramme et la biopsie cutanée confirment le rôle du tissu élastique dans les modifications de l'onde pulsatile artérielle chez les sujets athéroscléreux ou présentant une dégénérescence précoce du tissu élastique.

La perte de l'extensibilité des parois artérielles chez le sujet âgé a été démontrée par de nombreux auteurs dont BURTON (3) qui a mis en évidence le rôle du tissu élastique, après digestion trypsique de parois vasculaires, dans la morphologie du sphygmogramme artériel.

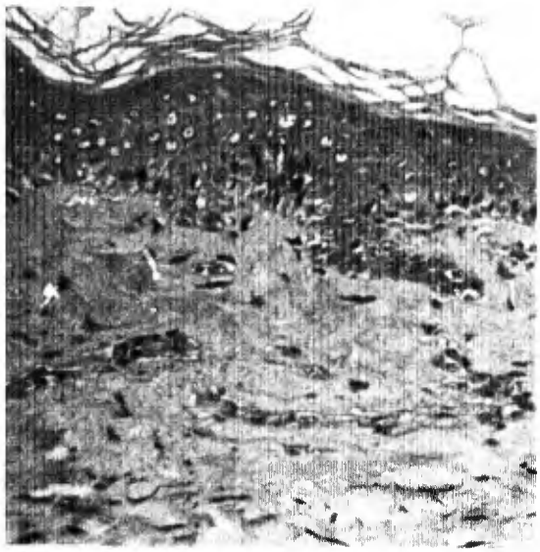
Conclusions

Le carotidogramme s'avère ainsi un moyen d'exploration de la pulsatilité du système artériel. Son interprétation, confirmée au besoin par la biopsie cutanée chez le sujet jeune, permet le dépistage et la surveillance du personnel navigant en assurant l'expert d'une parfaite adaptation cardio-vasculaire aux conditions de vol des pilotes.

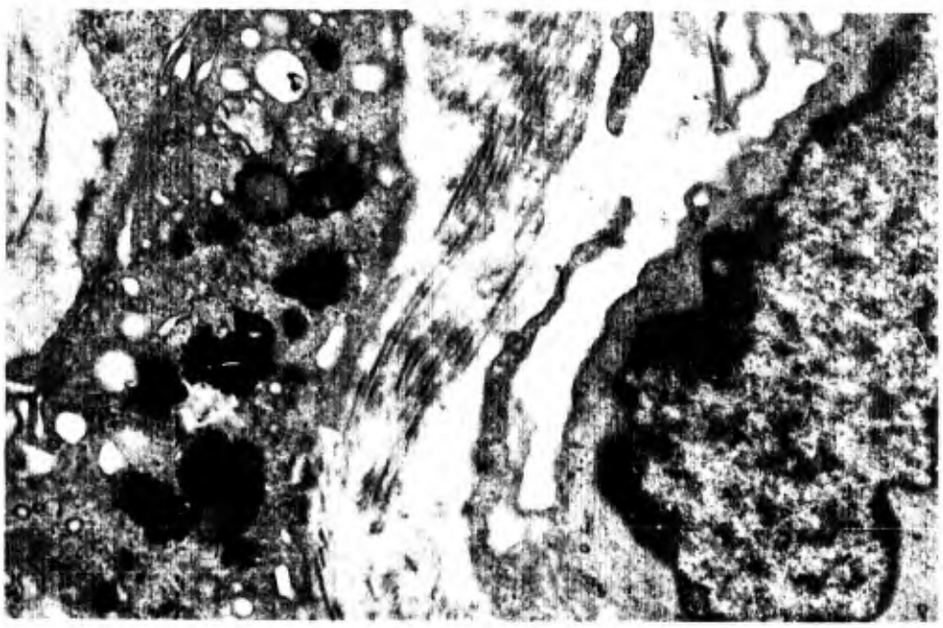
Soumis à un mode de vie particulier à bien des égards, à une hygiène alimentaire parfois difficilement adaptée, à des perturbations des rythmes circadiens, le Personnel Navigant représente un groupe particulièrement fragile et exposé aux désordres métaboliques favorisant le vieillissement.

Cette étude n'a pas permis d'apprécier les incidences de ces agressions multiples sur le vieillissement du Personnel Navigant. Elle apporte néanmoins une confirmation, celle de l'utilité des enregistrements mécanographiques au cours des examens de surveillance. Le carotidogramme comme l'a démontré la biopsie cutanée associée, apparaît un moyen d'évaluer l'âge biologique et de dépister les affections cardio-vasculaires dégénératives.

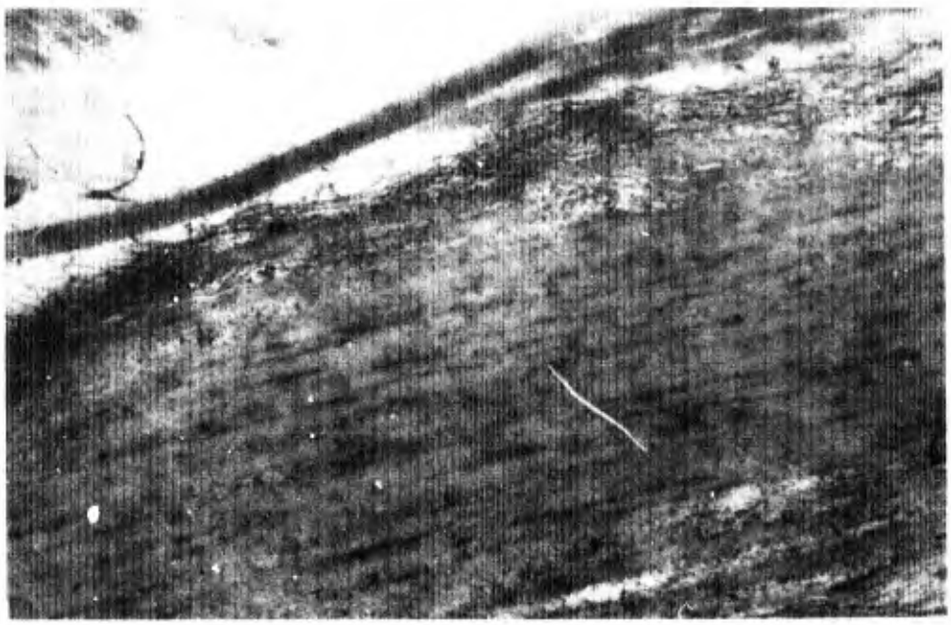
I - Début d'atrophie élastique avec constitution de la bande déserte sous-épidermique et persistance de quelques fibres élastiques papillaires, peau de type I.



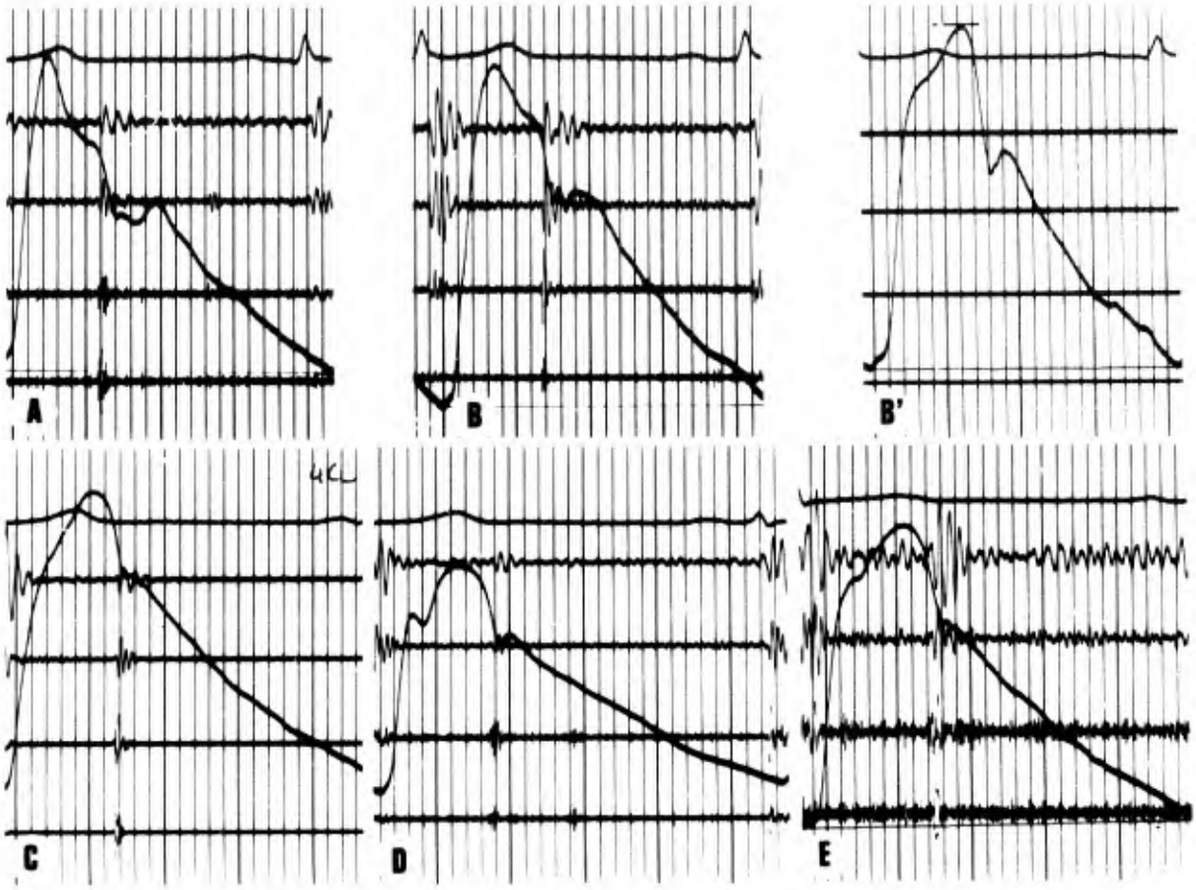
II - Atrophie élastique prononcée, bande déserte, épaisse et étendue, peau de type II.



III - Cellule fibroblastique riche en corps denses hétérogènes de nature lisosomiale - altérations mitochondriales associées. (G X 20000)



IV - Lame élastique constituée d'unités élémentaires bordées de microfibrilles - En bordure, fibre collagène avec sa situation périodique. (G x 60 000).



- Carotidogrammes -

A - sujet de 21 ans
B - sujet de 26 ans
B'- sujet de 32 ans avec montée lente dans la dernière partie

C - Sujet de 49 ans
D - sujet de 51 ans
E - sujet de 51 ans

- B I B L I O G R A P H I E -

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Le fibroblaste cutané au cours du vieillissement et de certains états pathologiques.
Annales Anat. Path., 1971, T 16, n° 4, 375-386.

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Masson Edit. PARIS, 1968.

4 - DANIELSEN L., KOBAYASI T.
Dégénération of dermal elastic fibres in relation to age and light-exposure.
Acta Dermatovener (Stockholm) 1972, 52, 1-10.

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Le vieillissement des cellules humaines.
Triangle 1974, XIV n° 2, 129-139.

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La sénescence 1 Approche du phénomène
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Thèse médecine PARIS 1974.

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DISCUSSION

The presented papers were discussed at two discussion sessions. The following is a summary of these discussion sessions.

Paper A3 entitled "COMMON PROBLEMS ENCOUNTERED IN LABORATORY SCREENING OF USAF FLIGHT CREWS FOR LATENT CORONARY ARTERY DISEASE", presented by Lt Colonel R. G. Troxler, USAF, MC:

Regarding the variables affecting cholesterol levels, the speaker has not studied the relationship of cholesterol levels to race in USAF flyers. In the management of hypercholesterolemic flyers the speaker has noted a lowering of cholesterol levels most often correlated with increased exercise and weight loss. This was also stated to be the experience of the French investigators. The French investigators were also concerned about the wide variability of cholesterol levels affecting the predictive ability of this risk factor for coronary artery disease. In their search for alternative predictors of coronary artery disease, they have been studying plasma fibrin derivatives and plasma protamines. The speaker had no experience with correlating these coagulation factors with coronary artery disease.

Discussion speakers: Fuchs (Ge), Colin (Fr)

Paper A4 entitled "EPIDEMIOLOGICAL STUDIES OF SUBCLINICAI DIABETES MELLITUS", presented by K. Reichenbach-Klinke, Major, MD, GAF:

The speaker was asked if he had done formal studies of statistical significance on the 10-fold increase in abnormal liver function tests in flyers with abnormal glucose tolerance tests; he stated he had not.

Discussion speaker: Troxler (US)

Paper A7 entitled "POSSIBILITE DE L'UTILISATION DES MOYENS DE SIMULATION DES AGRESSIONS AERONAUTIQUES POUR L'EXPERTISE MEDICALE DU PERSONNEL NAVIGANT", presented by J. Demange, le Medecin en Chef:

The speaker was asked if, in his experience, there was a correlation between heart to eye distance and G_z tolerance. He replied there was no correlation.

Discussion speaker: Clarke (US)

Paper A9 entitled "STUDIES ON STRESS IN AVIATION PERSONNEL: ANALYSIS AND PRESENTATION OF DATA DERIVED FROM A BATTERY OF MEASUREMENTS", presented by Dr. J. Robert Dillie:

Since the speaker found high levels of stress hormones in air traffic controllers correlated with the degree of difficulty of their jobs, he was asked if he had done similar studies in pilots, and if so could the hormone levels be used in selecting candidates for flying training. The speaker said that he had found extremely high levels of epinephrine in student pilots. Their levels were even higher levels found in combat pilots and astronauts. These levels were related to many factors, in one case with epinephrine levels four times higher than the highest level ever recorded in man; the student hated the instructor. In another case, it was related to the degree of competitiveness of the group. Due to the many different variables increasing stress hormones in student pilots the speaker has not yet been able to predict pilot performance from stress hormone levels.

The speaker was asked if he had studied urinary free cortisol as an indicator of stress in pilots. He said that he had not but that they have found that phosphatidyl glycerol does increase during stress.

Discussion speakers: Church (US), Henry (US)

Paper A10 entitled "THE FIELD ARTILLERY FIRE DIRECTION CENTER AS A LABORATORY AND FIELD STRESS-PERFORMANCE MODEL: I. POSITION PAPER; II. PROGRESS TOWARDS AN EXPERIMENTAL MODEL", presented by L. E. Banderet, Ph.D.:

The speaker was asked how he measured sleepiness in his study. He used the Clyde mood scale which is a self-rated mood scale of which sleepiness is one of six factors rated.

Discussion speaker: Reichenback-Klinke

Paper A15 entitled 'EVALUATION DE LA DISTENSIBILITE VASCULAIRE, DU DEBIT CARDIAQUE, ET DE LA CHRONOLOGIE CARDIAQUE, PAR LA MESURE DES VARIATIONS D'IMPEDANCE ELECTRONIQUE THORACIQUE', presented by Medecin en Chef J. Colin:

Because local skin resistances can vary widely in a given individual the question was asked whether the chest electrodes used to measure electrical impedance were affected by local skin resistance. The speaker replied they are not.

Discussion speaker: Caymaz (Tur)

Paper A16 entitled "THE INFLUENCE OF ALCOHOL ON SOME VESTIBULAR TESTS", presented by A. J. Greven:

One major point of the discussion was oriented toward establishing whether alcohol consumption could have an effect on the calibration procedures themselves and therefore influence the results. As pointed out by the author, these measures were repeated and appeared reliable.

The possibility was raised that since an externalized optokinetic drum requires foveation and presumably higher cortical function, that perhaps a test of the subcortical reflex with a drum rotating about the subject might reveal different results.

Due to individual differences in the tolerance to alcohol, the question of defining safe limits of consumption for the pilot could not be answered by these data. There was general agreement that since alcohol compromises visual tracking and other evidence indicates long-term vestibular changes under G-loading, that the ideal situation would be to abstain from alcohol when flying.

Discussion speakers: Lansberg (Neth), Von Baumgarten (Ge), Fuchs (Ge)

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15. Abstract

The clinical laboratory is indispensable in the practice of aerospace medicine. The optimal tests, techniques and procedures, along with their clinical correlations for judicious application are matters of continuing research and development. The AGARD Aerospace Medical Panel Specialists Meeting held in Ankara, Turkey, 23 October 1975, was directed towards improving diagnostic accuracy, enhancing utilization of diagnostic resources, and providing increased impetus toward standardization of clinical laboratory methods in aerospace medicine in the international community.

Papers were included on the following topics: Investigations on chemical, physical, physiological, radiographic and electrical test techniques, methodologies and applications in aerospace medicine; Research, development and evaluation of pertinent tests, techniques and procedures in aerospace medicine; Results of clinical and epidemiological application of these tests, techniques and procedures; Limitations of the tests, techniques and procedures due to variability, interference and inadequacies.

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