EARLY DETECTION
OF HEALTH IMPAIRMENT
IN OCCUPATIONAL EXPOSURE
TO HEALTH HAZARDS

Report of a WHO Study Group
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WHO STUDY GROUP ON EARLY DETECTION OF HEALTH IMPAIRMENT IN OCCUPATIONAL EXPOSURE TO HEALTH HAZARDS

Geneva, 10-16 December 1974

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EARLY DETECTION OF
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Report of a WHO Study Group

A WHO Study Group on the Early Detection of Health Impairment in Occupational Exposure to Health Hazards met in Geneva from 10 to 16 December 1974. Dr A. S. Pavlov, Assistant Director-General, opened the meeting on behalf of the Director-General.

Dr Pavlov said the purpose of the Study Group was to review the measures used in periodic medical examinations of workers to detect early health impairment and to make recommendations to governments and WHO with respect to the development of this field of preventive occupational medicine. He commented that in 1973, a WHO Expert Committee on Environmental Health Monitoring in Occupational Health made a recommendation to WHO requesting, inter alia, the development of a long-term programme in this field. The recommendations of that Committee were considered by the WHO Executive Board in January 1974, which decided to implement these recommendations in its resolution EB53.R23. A good deal of information is available on criteria for the early detection of health impairment from occupational causes; this can provide a valuable contribution to the early detection of diseases in general and to the field of preventive medicine as a whole.

He commented that the title of the meeting was quite broad and proposed that in the first instance discussions should be limited to the early manifestation of deviations from a state of health due to exposure to physical and chemical agents only. He recognized, however, the importance of biological and psychosocial factors at work, but suggested that these broad areas require separate consideration.

1. INTRODUCTION

One of the fundamental means of achieving the objectives of occupational health programmes is the detection of environmental conditions and biological changes that are forerunners of the early stages of health impairment. Because technical measures for such detection are not always available
and preventive measures are not always applied, there is still a need for early
detection of health impairment.

Extensive efforts have been made by different research institutes and
occupational health services throughout the world to develop methods for
such early detection. The WHO Expert Committee on Environmental and
Health Monitoring in Occupational Health in 1973 defined early detection as
"the detection of disturbances of homeostatic and compensatory mechan-
isms while biochemical, morphological, and functional changes are still
reversible". The Expert Committee recommended that "detailed guidelines
should be produced, with WHO assistance, for carrying out comprehensive
monitoring of workers' health to meet the different needs and resources of
industrialized and developing countries". This recommendation was
endorsed in a resolution adopted by the WHO Executive Board in January
1974.

The present Study Group is a first step towards the development of a
long-term programme, and will give an overview of the subject, emphasizing
the principles underlying health monitoring in occupational health pro-
grames. It is expected that in subsequent years guidelines will be prepared
in regard to changes in health parameters in humans exposed to various
occupational health risks.

The Group discussed only certain chemical and physical factors
that occur in the work environment. Other work factors, such as ionizing
radiations, biological hazards (e.g., occupational zoonoses), physical and
mental workload, climate, and psychological factors, were not discussed
but it is suggested that they might be the topic of special studies.

It should be noted that this report does not propose standards, but only
preliminary guidelines for use in occupational health practice. Emphasis
has been put upon those parameters that can be measured with techniques
that can be used in the setting up of occupational health programmes, and
that have proved their value in occupational health practice. Some mention
is made of other health parameters, which are often highly non-specific and
sometimes need to be measured by very advanced techniques, still outside
the scope of occupational health practice; moreover, their significance for
actual or impending health impairment has not yet been adequately estab-
lished in many cases.

More detailed and extensive guidelines should be incorporated in the
long-term programme; the elaboration of such guidelines should be linked
with programmes for establishing maximum permissible limits for occupa-
tional exposure.

2. HEALTH IMPAIRMENT

Health does not mean only absence of disease but also optimum physical, mental, and social wellbeing. Health is not something that one possesses as a commodity, but connotes rather a way of functioning within one’s environment (work, recreation, living). It not only means freedom from pain or disease, but also freedom to develop and maintain one’s functional capacities. Health develops and is maintained through interaction between the genotype and the total environment. The work environment constitutes an important part of man’s total environment, so health is to a large extent affected by work conditions.

However, the definition of health and the objectives of occupational health should be made more operational. Objectives may range from prolongation of life expectancy and minimizing the incidence of incapacitation, disease, pain, and discomfort, to more subtle improvements of physiological abilities in relation to sex and age, including preservation of reserve capacities and adaptive mechanisms, provision of levels of individual achievement, including creative subjects, improvement of physical and mental ability, and adaptability to changing circumstances of work and life. In a work organization these abilities may be evaluated quantitatively by indices of absenteeism, job satisfaction, and work stability.

Impairment of health involves a reduction in functional abilities, either through a direct cause-effect relationship or through an indirect conditioning. For example, exposure to silicon dioxide may cause silicosis as a direct effect, whereas exposure to dust may co-determine the course of chronic bronchitis without necessarily being the principal cause of this disease; no silicosis occurs without silica, but bronchitis is possible without dust. Again, acute effects of chemical agents inducing small and rapidly reversible functional disturbances (e.g., changes in psychological and neurophysiological condition, especially attention) may be indirect causes of accidents.

Such impairments of health need not necessarily be present at the time of a medical examination, but some biological changes may be present that predict the occurrence of functional disablement in the future, if working conditions are not changed, e.g., slight radiographic changes may predict disabling pneumoconiosis, a dip in the audiogram may predict occupational deafness. A decreased reserve capacity should also be regarded as a limita-
tion of functional capacity. Functional impairment need not necessarily be apparent to the subject himself.

Health may be impaired not only by the presence of hazardous factors (sometimes called overload) e.g., toxic agents, noise, silicon dioxide, but also by the absence or deficiency of environmental factors (sometimes called underload) e.g., lack of sufficient muscular activity, deprivation of communication with other people, lack of variability in work tasks, lack of individual responsibility, and lack of intellectual challenge. Although little is known about some of these conditions (deficiencies in essential stimuli), health evaluation should consider both the overload and the underload aspects of work conditions. However, it must be admitted that up to now relatively little is known regarding the health effects of underload.

2.1 Criteria of health impairment

Criteria of health impairment should if possible be based upon early reversible changes that predict the occurrence of manifest signs and symptoms, in order to make prevention of overt disease or disablement possible. One may distinguish the following broad overlapping categories of criteria:

1. Changes in biochemical and morphological parameters, to be measured by laboratory analysis, e.g., parameters of disturbed porphyrin and glutathione levels in exposure to lead; inhibited cholinesterase activity in exposure to organophosphorus insecticides; changes in the levels of various serum enzymes; changes in metal concentrations in body fluids; chromosome aberrations; or abnormal sputum cytology. Some changes are detectable only after loading tests, e.g., biliary excretion of dyes, or by other special tests.

2. Changes in the physical state and the function of physiological systems, to be evaluated by physical examination, and by means of loading tests, e.g., pallor, stooping posture, and changes in ECG tracings, in physical working capacity, in higher nervous function, or in reproductive function.

3. Changes in well-being to be evaluated by medical history taking and questionnaires, e.g., drowsiness, irritation of mucosa on exposure to solvents.

4. Integrative changes that may result from effects on several physiological systems: more so than the previously listed changes, they are not specific and are affected by factors unrelated to work, e.g., nutrition, communicable diseases. However, they may be important in health evaluation for elucidating work-related health effects and may at times be the only available evidence of an effect. In individual cases, it may not be possible to sub-
Initiate their relationship to work factors unless, for example, the time course of events in relation to exposure is highly suggestive. However, in epidemiological surveys with adequate study design, these integrative changes may indicate the beginning of health impairment due to work factors.

Examples are changes in:

— subjective state, the incidence and prevalence of which can be measured objectively in groups of workers (often the help of psychologists or sociologists is needed to prepare adequate questionnaires);
— behaviour, e.g., excitation, drowsiness, depression, personality changes;
— anthropometric measures, e.g., height, weight, girth;
— employee records, e.g., accidents, sickness, absenteeism;
— medical statistics, e.g., hospital admission rates, mortality rates.

These integrative changes may often be the first indication of hitherto unexpected causes of ill-health that require more detailed observations. In addition to being potential indicators of work-related factors, they may also be useful in providing insight into the general health of the working population as determined by the general environmental or socioeconomic conditions.

2.2 Health significance of work-related effects

Impairment of health involves a limitation of functional capacities. However, not all effects of a workload necessarily have a bearing on health as defined above.

Information available on methods used in establishing permissible limits for toxic substances in work-room air may serve to elucidate the difference between effects (or responses) as such and health impairment.

Even though different scientific authorities may not fully agree upon what should be called "health impairment", it can be stated that a statistically significant effect as such is not the same as impairment of health; one should therefore distinguish between effects as such and adverse effects, i.e., unacceptable effects. What is regarded as unacceptable (not permissible) is a matter of interpretation and ultimately of choice. Whereas the concept of health and of adverse effect may differ from country to country, exposure-effect/response relationships will to a large extent be similar (taking into account the variability discussed in section 4), whatever decisions are made. Effect as such is a neutral concept, whereas adverse effect and health impairment are not neutral concepts. It should be realized, however, that

there is usually a continuum: no observed effect—compensatory effect—early effect of dubious health significance—early health impairment—manifest disease.

Because of the rather broad definition of health impairment, the relevance of effects in regard to health cannot always be agreed upon. The individual occupational physician monitoring health parameters in the working populations entrusted to his care, often has to define this relevance himself.

This point has been elaborated in regard to toxicological effects; however, in regard to other potentially hazardous workloads, the same divergence of opinion exists: Is a noise level of 85 dB(A) acceptable, disregarding nuisance, disturbed communication, and autonomic effects? Does one accept that hypersensitive or hypersusceptible workers should be transferred to another department, because they cannot cope with their workload, or should the workload be adapted even to the most hypersusceptible and hypersensitive worker, so that he is not forced to leave a maybe highly appreciated social group of fellow workers?

Whatever the decisions as to health impairment in a country are, there will always be three types of effect to be distinguished.

1. Effects agreed by general consensus to be adverse, e.g., in lead exposure, an aminolaevulinic acid (ALA) level of 20 mg/litre in urine; in noise exposure, an overt dip in the audiogram.

2. Effects that may be considered to be adverse, although adequate epidemiological proof is not available, e.g., in exposure to lead, subclinical decrease of nerve conduction velocity; in noise exposure, temporary auditory threshold shift.

3. Effects possibly related to exposure and to health impairment, but about which there is no consensus, e.g., in lead exposure, change in hydroxyindoleacetic acid excretion; in noise exposure, relationship to presbyacusis.

Routine medical examination in occupational health should certainly aim at elucidating type 1 effects, and if possible also type 2 effects; the test battery has to be devised accordingly. Type 3 effects are still the subject of scientific research and need not necessarily be included in routine health monitoring.

The employer and the authorities should provide adequate facilities for the detection of types 1 and 2 effects. At the same time, they should provide the means for advancing knowledge through scientific research. The report of the WHO Expert Committee on Environmental and Health Monitoring in Occupational Health concluded that: "It is necessary to educate both management and workers to promote the introduction and expansion of occupational health services and monitoring programmes,
3. HEALTH EVALUATION

This report discusses in detail the principles of health evaluation programmes, i.e., the systematic examination of the working population itself in order to prevent health impairment.

It has been emphasized that environmental and health monitoring needs to be carried out for the following reasons:

— to assess occupational health risks;
— to identify occupational health risks not previously recognized;
— to reveal other sources of health risk;
— to identify and promote work factors that are beneficial to health;
— to provide information on community health problems.

Health evaluation may follow two approaches:

— evaluation of (precursors of) health impairment, emphasizing where possible the detection of early and reversible effect;
— evaluation of exposure; this may indirectly indicate the presence of precursors of health impairment if dose-effect/response relationships are known.

In practice both approaches are often followed at the same time, e.g.,
determination of lead in blood and protoporphyrin in erythrocytes (PPE),
determination of lead and aminolaevulinic acid (ALA) in urine. Moreover, indices of exposure may also be affected by changes in physiological function, e.g., increased cadmium excretion in the urine if kidney function has been impaired.

Both approaches serve the prevention of health impairment. One has to measure those parameters that can serve as a warning signal for impending risks, i.e., one has to rely, whenever possible, on early reversible changes in biological parameters, occurring in the early phase of the dose–response relationship, before health impairment has become manifest. Several tests can be used to indicate and evaluate or to detect impending health impairment.

3.1 Health evaluation versus environmental evaluation

Both types of evaluation have their place in the prevention of health impairment; they are not mutually exclusive, but complementary.

Environmental evaluation can be used only to anticipate the risk of health impairment, but not to detect such impairment, to identify workers showing undue susceptibility, or to reveal trends in the health status of workers.

Biological assays appear to be, in special cases, much more reliable indicators of health risks than are measurements of air contaminants. In cases of physical workload, it is usually impossible to measure the external physical load, except in some specific situations, whereas measurement of a few physiological parameters readily provides information on the total workload and its acceptability.

Health evaluation procedures have some evident advantages: they automatically take into consideration all the variables and make possible good estimates of the effective integrated exposures to air contaminants (uptake through lung and skin and gastrointestinal tract; integration of variation of air concentrations, etc.).

It should be noted that periodic health evaluations will never be adequate to prevent acute intoxications in the case of sudden high exposure. They serve mainly to prevent adverse effects of chronic exposure. However, if there is a long latency period between exposure and ultimate response (e.g., in the case of malignant tumours), and if no reversible early indicators are known, periodic surveillance will be of no avail.

The establishment in recent years of permissible limits for toxic substances in biological specimens can be considered an important contribution to the prevention of occupational health impairment. In some cases, they even provide more adequate health protection than permissible limits for toxic agents in air.

3.2 Significance for community health

Occupational health can be defined as aiming at health protection and health promotion for the gainfully employed, and at the adaptation of work to man and of each man to his job. Both approaches indicate the relevance of occupational health data for a better evaluation of community health.

The occupational environment reflects to a large extent the present and future state of the ambient environment, although with differences in intensity and duration of various exposures. Environmental hygiene can be

regarded, in many senses, as a daughter of occupational hygiene, particularly in the field of ambient air pollution and noise exposure. Occupational health practice evaluates the effects of these work factors on the health of selected groups of regularly supervised workers. The information thus obtained is valuable in protection of community health, if due allowance is made for differences in intensity and duration of work factors and in host factors.

If one takes the broader definition of occupational health, the relevance for public health is even more impressive. The working population constitutes a substantial part of the total adult population. Health monitoring, e.g., measurements of the prevalence of infectious diseases, nutritional status, and physiological capacities, will yield a valuable body of data for the evaluation of the health status of the total population concerned.

It should be recognized that, especially in the last decade, community health work has started to adopt a similar approach to that discussed in this report: electrocardiographic tracings, analysis of blood lipids, and blood pressure measurements for the early detection and prevention of cardiovascular disease; immunological studies for the early detection of rheumatoid diseases; lung function studies in heavy smokers; blood pepsinogen levels as indicators of a risk of gastrointestinal ulcers. There is often a lack of occupational health services where communicable diseases are still prevalent and increasing amounts of pesticides are being used. Occupational and community health workers should join forces to achieve more effective prevention of such widely occurring and often life-threatening diseases as those mentioned above. Where possible, community health programmes should make use of the work organization of modern industry; this could greatly enhance the effectiveness and efficiency of such programmes.

4. INTER-INDIVIDUAL AND INTRA-INDIVIDUAL VARIABILITY

In occupational health evaluation programmes it should be recognized that there are large differences in response between various subjects for similar exposure. Evaluation of this variability could be one of the objectives of a health programme, serving ultimately to protect not only groups of subjects but also susceptible individuals within these groups. Moreover, the variability in response and also in exposure largely determines the design of a health programme.

In animal experiments, effects are usually expressed in averaged data, e.g., for body weight, liver weight, haemoglobin level, blood pressure, excretion of catecholamines; in studies of carcinogenicity, mutagenicity,
and teratogenicity, or of exposure to fibrogenic dusts, the relative number of animals affected may be given. Animals are usually taken from a well-bred stock, with as little difference in genotype as possible; environmental conditions are controlled and are similar for all animals, except in regard to the exposure under study.

In studies of workers the same procedure is often followed; the variability in susceptibility is assumed to be normally distributed, with a small coefficient of variation.* However, it cannot be stressed too strongly that inter-human variability is much larger than intra-species variability in experimental animals.

In setting health standards (permissible levels of exposure to chemicals, of workload, of noise levels, of psychosocial stress, etc.) for the working environment, one should not gear the permissible levels to the non-existent "average human being ", but to the actual workers at risk, taking into account variability in exposure and in response. Therefore, in the prevention of health hazards in groups of workers, one should first evaluate the exposure-response relationships and then, after having screened out the workers at risk, study the exposure-effect relationship in such individuals, as discussed in section 5.

When studying health parameters in groups of workers, it is preferable to make use of individual data, combined into a stratified frequency (percentile) distribution. This makes it unnecessary to assume a normal distribution, as may usually be done in animal experiments; it shows quite clearly the number of subjects at risk within the exposed workers’ population. In the case of exposure to lead, it is not the average level of lead in the blood that is important, but the number of subjects whose blood level exceeds a certain value (e.g., 70 µg/ml) or whose level of ALA in the urine exceeds 10 mg/litre. Similarly, in the case of a physical workload, it is the number of subjects with a blood pressure of more than 180 mm Hg that is important, and in the case of a heat load, the number with a sweat loss of more than 1 litre per hour. The validity of the tests is determined quantitatively on the basis of the individual data and the frequency distributions, as described in section 5 (see page 21). This is the only way of making due allowance for variability of response when designing preventive measures.

It is necessary to distinguish between intra-individual variability, i.e., variability in the same individual, and inter-individual variability, i.e., variability between individuals. The factors that determine this variability and their relevance to health surveillance are discussed below.

* The coefficient of variation is the standard deviation (σ) divided by the mean (x), expressed as a percentage, i.e., coefficient of variation = \( \frac{\sigma}{x} \times 100 \).
4.1 Enogenous factors influencing variability

4.1.1 Age

Older subjects with decreasing cardiovascular capacity are more likely to show electrocardiographic abnormalities than are younger subjects when they are exposed to carbon monoxide or when they are under a high physical workload. On the other hand, among older workers, considerable selection may have taken place, the more susceptible subjects having already left the work because they experienced discomfort or became ill. In pregnant women, it has to be remembered that the developing embryo may be more susceptible to noxious agents than the exposed mother (e.g., in the case of methylmercury poisoning).

4.1.2 Sex

Females probably experience more subjective annoyance from noise than males. In a human volunteer study on lead toxicity, adult females were shown to respond with an increase of protoporphyrin in erythrocytes at lower levels of lead in blood than adult males and with a steeper dose-effect curve. Because of different anthropometric measures, females may be less suited for some work tasks than men and more suited for others; pregnancy may decrease the capacity to cope with many work factors.

4.1.3 Genotype

The importance of biochemical individuality has been stressed by Williams. If one studies the variability of enzyme activity or other biochemical "constants" in blood in a group of "normal healthy" individuals, there will be a distribution regarded as "normal"; most individuals will have levels around the median or the mean, but some will have considerably higher levels. However, such a group range is a summation of individual ranges; the intra-individual variability is bound to be much smaller than the intra-group variability. For example, the normal leucocyte count varies from about 3000 to 13 000 per mm$^3$ blood. This figure is based, however, upon individual ranges of say 3000–4500, 6000–7800, 9000–12 000 leucocytes per mm$^3$. A leucocyte count of 4000 per mm$^3$ may be quite "healthy" for some individuals, but may indicate a health risk in others; it certainly indicates a deviation from health if used as a group mean. It is well known that the cholinesterase level in subjects not exposed to organophosphorus

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insecticides covers a wide range; an acceptable decrease of 25% in the group
mean or median may overlook a decrease of, say, 50% in a few subjects.
The same will probably be true for many, if not for all, biological parameters.

Special cases of biochemical individuality have been studied. Specific
genetic variations occur in some workers, making them more susceptible
to certain chemicals than "normal" persons. These include: haemoglobin
abnormalities, such as sickle-cell anaemia and the sickle-cell trait (susceptibility
to low atmospheric pressure); glucose-6-phosphate dehydrogenase
deficiency (susceptibility to certain drugs, and to naphthalene, trinitro-
toluene, phenylhydrazine, and possibly lead); serum trypsin inhibitor
deficiency (possible association with occupational lung); cholinesterase
variants (possible susceptibility to organophosphorus insecticides); and
reduced metabolic capacity for tetraethylthiuramdisulphide (possible sus-
cceptibility to carbon disulphide).* It is well known that chronic non-specific
lung disease (asthmatic bronchitis, chronic bronchitis, emphysema, etc.)
also has a genetic basis; susceptibility to occupational dusts may determine
the risk to health.

Similar considerations apply to lung function tests. It has been noted
in this respect that there is a consistent physiological difference in ventilatory
capacity between Europeans on the one hand and Africans and Asians on
the other. In males the average ventilatory capacity has been found to be
0.45 litre/s lower in Africans and Asians than in Europeans.

The above-mentioned genetic patterns are not evenly distributed, but
may tend to occur predominantly in certain countries, even in certain ethnic
groups. Pre-employment tests have been devised to single out the potentially
hypersusceptible workers, in order to prevent occupational poisoning in
concentrations lower than those known to have a toxic effect. However,
there is still insufficient epidemiological evidence to support the use of these
tests as definite criteria of suitability for employment.

The above-mentioned biochemical individuality may lead to differences in
toxicokinetics and thus affect the time courses of absorption, distribution,
metabolism, and excretion of chemicals throughout the body, and so leading
to different levels of the toxic agents at the effector site, even although
external exposure is similar. Differences in the rate of induction of meta-
bolizing enzymes may be one of the factors. It is well known that the
biological half-lives of drugs are more similar in identical twins than in
non-identical twins. Up to now, this aspect of enzyme induction has been
studied mainly in regard to drug metabolism, and hardly at all in the field
of occupational toxicology. Differences in the type of respiration may be a

actor determining the dosage to the lungs and the magnitude of lung deposition and absorption. In one study, the inhaled dose of calcium carbonate dust was determined in three subjects following (a) a normal quick inhalation and slow exhalation, and (b) the opposite type of respiration; the inhaled dose increased with the higher inspiratory flow velocity. Thus, a similar environmental exposure, in respect of concentration, particle size, and duration, gave a considerably different dosage to the lungs.\(^a\)

### 4.2 Exogenous factors influencing variability

#### 4.2.1 Nutrition

The effects of various nutritional regimes (deficiencies of calcium, phosphorus, iron, and protein in rats exposed to lead) has been studied.\(^b\) Marked changes were observed in the rate of absorption and distribution of lead throughout the body. There is suggestive evidence that at least iron deficiency may play a role in raising protoporphyrin levels in erythrocytes in children and females exposed to lead.\(^c\) Adequate intake of vitamin C enhances enzyme induction. That nutrition (undernutrition, overnutrition, malnutrition) may influence physical working capacity has been amply demonstrated. Malnutrition may affect the metabolism of toxic agents and also the tolerance mechanisms, e.g., cholinesterase activity appears to decrease in cases of malnutrition.\(^d\)

#### 4.2.2 Past or present disease states

Although there are many examples of disease not caused by the work conditions under study but influencing susceptibility to these conditions, only a few are mentioned: tuberculosis in workers exposed to silicon dioxide; parasitic liver disease and exposure to heptotoxic agents; malnutrition or chronic malaria and exposure to a heavy work load; parasitic anaemia and exposure to lead. The potential effects of pharmaceutical substances (drugs) on workers exposed to toxic chemicals should also be mentioned. This problem has so far been insufficiently studied. Drugs may affect enzyme induction and hence the metabolism of toxic agents; conversely, toxic agents may affect the metabolism of drugs.

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4.2.3 Previous or concomitant exposure

Previous exposure at work or concomitant exposure outside employment to the same work factor may produce cumulative effects. This applies not only to chemicals but also to noise, fibrogenic dusts, and even excessive physical exercise (possibly a combination of work and recreation) and sustained mental effort (information processing during work and during study outside working hours, particularly in younger workers).

Combined exposures are important, although limited research has been performed on this topic. There is evidence that simultaneous exposure to certain chemical agents and heat leads to increased toxicity in experimental animals,\(^a\)\(^b\) and in humans where work involves exposure to toxic substances together with physical stress.\(^a\)\(^b\) Furthermore, there is experimental evidence in humans that a combination of mental stress and noise has a synergistic effect on blood pressure. There is ample proof that the physical workload largely co-determines the response to chemical exposure. In the case of exposure to carbon monoxide, the increased oxygen demand created by physical effort further increases the hazard; this effect is particularly serious at high altitudes.

4.2.4 Social conditions

Housing, crowding, nutrition, mode of transportation, necessity for extra earnings, etc. are often clearly related to the prevalence of disease states, body weight, height, and even life expectancy. In many regions, ambient industrial air pollution is high, thus increasing the total exposure of the workers.

There tend to be differences in exposure, even for workers performing the same work, owing to differences in patterns of movement, in experience in handling the work task, in personal cleanliness, etc. There may easily be a considerable range in personal exposure, with some workers more at risk than others. This applies not only to chemical exposure, but also to physical workload, heat load, noise exposure, etc.

There are many possibilities of intra-individual and inter-individual variability in the relationship between exposure (workload) and the effect/response. With decreasing load, more and more attention needs to be paid to personal factors, rather than to work factors alone. With a grossly


unacceptable workload, all workers will suffer health risks: with improved working conditions the focus of preventive action shifts to individuals and to subgroups. "Abnormal responses" are often mistaken for imaginary or neurotic syndromes, whereas in reality there is a biological basis for the abnormal exposure–effect relationship.

One should distinguish between hypersusceptibility and hypersensitivity. In hypersusceptible persons, "normal, expected" effects occur, but with a lower exposure than in the majority of workers: the threshold is lower and the exposure–effect curve may be steeper, so that the difference is a quantitative one. In case of hypersensitive persons, "allergic" effects occur after preconditioning by exposure; the difference is therefore a qualitative one. For chemical agents with low molecular weight, the probability of sensitization will be related to the degree of reactivity of the compound and to the degree of exposure. However, if sensitization has already occurred, even minimal exposure of the skin or respiratory system may lead to clinical manifestations. In the case of hypersusceptibility, prevention of health impairment may be achieved by reducing the exposure. Prevention of a recurrence of allergic symptoms usually necessitates a transfer to other work situations. Although in modern industries allergic skin diseases may constitute a large part of the occupational diseases, they demand a preventive approach so completely different from that required for "normal" exposure–effect/response relationships that its discussion is outside the scope of this report.

5. EPIDEMIOLOGICAL METHODS IN OCCUPATIONAL HEALTH EVALUATION

Although in different settings the evaluation of occupational health programmes may make use of different testing procedures, since these will be determined by specific local needs and possibilities, some principles will have to be adhered to in all instances. A few aspects of the design of occupational health evaluation programmes are discussed below.

5.1 Exposure–effect/response relationships

For the successful prevention of occupational health hazards, it is necessary to know the quantitative or, at least the semi-quantitative, relationship between the magnitude (intensity and duration) of the work factors (chemicals, noise, physical load, heat load, psychosocial stress, etc.) and the resultant health effects.

There are two ways of expressing such a relationship:

1. If in an individual the hazardous work exposure increases in intensity and/or duration above a threshold level, the probability of health impairment may increase:

   — there may be an increase in the severity of a qualitatively specified impairment, e.g., eye irritation, headache, raised SGPT and SGOT levels, raised blood pressure, increased heart rate, increased oxygen consumption;

   — more types of impairment may occur, each with its own threshold level of exposure, e.g., in case of noise, at 60–80 dB nuisance symptoms and autonomic disturbances, and at 90 dB also a dip in the audiogram and occupational deafness; in case of asbestos, high levels of exposure cause asbestosis, slight to moderate exposure only mesothelioma; low to moderate exposure to styrene results in irritation of the mucosae, intensive exposure causes drowsiness and ultimately unconsciousness;

2. If in a group of subjects hazardous work exposure increasingly exceeds the "threshold level", the number of workers with a specified biological effect increases, and within this group some individuals react with a more severe effect or with more types of effect. The variability in susceptibility to a specified exposure comes into play. For example, in a group of workers with similar exposure to mercury, only some subjects will show signs and symptoms of poisoning and the percentage of such workers will increase with exposure. Similarly, after physical exertion only a few older individuals may show ST-depression in the electrocardiogram.

It is therefore possible to distinguish:

(a) exposure–effect relationship, i.e., the relationship between exposure and severity (quantitative) of a qualitatively specified health effect in an individual (graded effect);

(b) exposure–response relationship, i.e., the relationship between exposure and the relative number (percentage) of individuals with a qualitatively specified severity of a qualitatively specified effect in a group of subjects (quantal response).

There are differences between individuals in the exposure–effect curves, owing to such factors as age, sex, intercurrent disease, genetic make-up, nutritional deficiencies, etc. The curves differ in no-effect-level and in steepness. For a group of workers, this inter-individual variability manifests itself in the exposure–response curve. For the prevention of hazards in workers as a group, the use of exposure–response curves is to be preferred;
for the prevention of hazards in susceptible individuals, exposure–effect relations have to be known.

5.2 Validity of tests

Tests may be indicative of three situations with respect to time:

1. Current events, i.e., tests may indicate the probability of exposure or of changes in the functioning of biological systems at the moment of investigation, e.g., cholinesterase levels in blood indicative of exposure to organophosphorus insecticides; trichloroacetic acid levels in blood or urine indicative of trichloroethylene exposure; dips in the audiogram indicative of exposure to high noise levels; sweat loss as an indicator of heat load; alcohol level in blood as an indicator of disturbed psychomotor performance.

2. Past events, i.e., tests may indicate the probability of exposure or disturbed function in the past, e.g., malignant tumours may develop many years after occupational exposure to some aromatic amines or asbestos; atherosclerotic disease may develop as a sequel to exposure to carbon disulfide; bone necrosis may be a sequel to vibration. Tests indicative of past events may point to a lack of preventive measures. They may, however, also reveal the previous presence of hitherto unknown hazards, thus making possible the prevention of health impairment in future cohorts of the working population, e.g., the recent indications of a relationship between angiosarcoma of the liver or thrombopenia and previous exposure to vinyl chloride.

3. Future events, i.e., tests may indicate the probable occurrence of disturbed functions or of disease in the future, if work conditions are not improved, e.g., ALA in the urine as a predictor of impending intoxication with inorganic lead; X-ray abnormalities as predictors of silicosis and asbestosis; a dip in the audiogram as a predictor of hearing loss or of social alienation as a consequence thereof; lowered response threshold to cold as a predictor of Raynaud’s syndrome.

Parameters of exposure are usually rather specific for the exposure itself, although such an exposure may have taken place outside the working area, e.g., carboxyhaemoglobin in the blood may result from occupational exposure, inhalation during commuting, or smoking; pesticide levels in the blood or fatty tissue may be due to occupational exposure, to ingestion of pesticides with food, or to their handling during home gardening.

Parameters of response often are non-specific for the exposure factor under consideration or for the disturbance of certain biological systems, e.g., anaemia may be due to blood loss, to iron deficiency, or to exposure to lead
or benzene; leucopenia may be due to benzene exposure, to ionizing radiation, or to certain pharmaceutical drugs; electroencephalographic abnormalities may be due to chlorinated hydrocarbon pesticides or to epilepsy; dips in the audiogram may be due to occupational noise, to military service, or to the noise of discotheques; changes in lactate dehydrogenase may be due to disturbed liver function or to cardiac disease; changes in the electrophoretic protein pattern may occur in liver disease, kidney disease, or malnutrition.

It is therefore important to be aware that the indicative value of biological tests should always be determined before they can be used in routine occupational health evaluation. For this purpose it is necessary to undertake occupational epidemiological investigations and to study health parameters in relation to work factors in groups of workers, taking into account endogenous co-determining factors (e.g., age, sex) and exogenous ones (e.g., socioeconomic situation, nutrition).

The Group agreed that the validity of the tests to be applied in periodic health surveillance of workers should be quantitatively determined. For the purpose of the Group’s discussions, the following definitions were adopted, based on those proposed by MacMahon & Pugh.:

**Validity**: the extent to which subjects in a case-control study are correctly classified or the extent to which a situation as observed reflects the true situation, e.g., how well the distribution of carboxyhaemoglobin levels in a group of workers reflects occupational exposure to carbon monoxide after taking into account other sources of carbon monoxide intake; prevalence of lung cancer in workers in relation to radon exposure, after taking into account smoking habits. Validity consists of two components, sensitivity and specificity.

**Sensitivity**: the extent to which persons who truly manifest a particular characteristic are so classified. There is a low probability of false negative data, e.g., examination of workers exposed to inorganic lead by means of a questionnaire only will result in many subjects being declared “healthy”, whereas laboratory examination (e.g., haemoglobin determination, ALA in the urine) may reveal many more affected workers; physical examination alone may result in patients with lung carcinoma being pronounced healthy; and, again, physical examination alone will not reveal typical bone necrosis due to “caisson” disease.

**Specificity**: the extent to which persons who do not manifest a particular characteristic are correctly classified. There is a low probability of false positive data, e.g., workers who do not have manifest inorganic lead

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Intoxication will be expected to have ALA in the urine at concentrations of less than 10 mg/litre; workers without noise deafness will not be expected to show dips in their audiograms.

Sensitivity and specificity can be expressed in quantitative terms. In one method, each term is expressed on a scale ranging from zero to one (maximum), the validity being the sum of the two values and thus, ranging from zero to two. Many examples of the use of this approach in epidemiological toxicology were provided; a validity of 1.80 was regarded as an indication of a valid prediction. With regard to the two components of this figure, it should be noted that when it is important to determine whether there is a real threat to health, the sensitivity should approach one, even at the expense of specificity; in this case one wants to be sure of finding all the subjects exposed to, or responding to, a particular hazard, and is prepared to accept a large number of false positives, e.g., in case of carcinogenic risks. If on the other hand, one is not concerned about missing positive cases and if limited means for surveillance are available, one will prefer highly specific tests.

5.3 Cross-sectional and longitudinal studies

For the purposes of routine health surveillance in occupational medicine, scientific research is needed not so much to advance the frontiers of knowledge as to apply existing knowledge to the prevention of impending or actual health impairment. Nevertheless, some epidemiological principles should be adhered to in carrying out routine health monitoring. The mere observation that health impairment occurs in workers exposed to potentially hazardous working conditions does not necessarily prove a relationship. Particularly in the case of parameters that are not highly specific, a cause-effect relationship may be deduced all too easily.

One of the basic principles of epidemiological studies is to provide adequate control values. The occupational physician responsible for health monitoring should always try to compare parameters established in exposed workers with those in workers not exposed to the work factors under study. Two approaches are possible.

1. A cross-sectional study of a group of workers, i.e., assessment of the health status of the exposed group at a certain point in time. In such studies the distribution of health parameters in other groups of workers not exposed to the same working conditions must be known, through an examina-

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tion of them at the same time, through previous knowledge of what is "normal" in non-exposed workers, or—particularly in the case of rather specific parameters—from the literature. A note of caution should be given: literature data on "normal" levels may be highly dependent upon the analytical methods used and upon the population examined. The occupational health physician should therefore know what would be the distribution of levels in his workers if they were not exposed and were measured by the same techniques as applied in his routine health monitoring.

The "normal" levels should be established in workers who are similar in as many aspects as possible to the worker group eligible for monitoring. Endogenous and exogenous factors that may determine health parameters have been mentioned in section 4. The control group should be comparable at least in respect to sex, age, and socioeconomic and ethnic status. For example, it is often inadmissible to compare health parameters in foreign "guest workers" with those of the indigenous population and vice versa.

One special possibility of making up adequate control groups should be mentioned: the use of "matched controls". i.e., for each exposed worker one or two non-exposed workers of about the same age, sex, duration of employment, educational level, socioeconomic group, and place of living, are examined. In this way, each exposed worker is compared with his paired worker. Testing the statistical significance of differences in health parameters in matched pairs yields a much more sensitive procedure than if combined data from groups of workers are tested. The use of this technique is particularly desirable in the case of small groups of exposed workers or in the case of only slight deviations in health parameters.

Cross-sectional studies should be repeated at certain intervals with the same or with comparable test procedures, the length of the interval being determined, for example, by the severity of potential health risks, stability and intensity of workload, and stability of the work population.

2. A longitudinal study, i.e., a comparison of the change in health parameters within each individual in the course of time. This is another form of a matched control study; the worker is matched to himself, the various examinations taking place at different points in time.

This method is to be preferred to the cross-sectional study because it more readily detects deviations in health parameters. Because of the individuality of response, even a relatively small change in health parameters may become manifest, although such a change is still within the "normal" group range. Special sensitive statistical techniques are available to test the significance of differences in the course of time, either in the data on one individual or in grouped longitudinal data.
This approach does not require the examination of non-exposed controls, except in the case of parameters that are also affected, for example, by age and season. Thus, it saves financial expenditure and use of manpower. The test procedures should remain the same or yield comparable data.

Longitudinal surveillance should start at the pre-employment examination, or at least at the start of the exposure under study, in order to provide baseline data from a period of non-exposure.

5.4 Criteria for selection of tests

The choice of tests for examining groups of workers is limited for practical reasons, particularly in the case of routine evaluation:

- the test should not demand an undue expenditure of time by the subjects examined or by the medical and laboratory staff; the test should not be unnecessarily expensive with regard to supplies, equipment, and staff;
- the test should not carry a risk to health and should not be inconvenient to the subjects examined;
- the test data should be in the relevant range of occupational exposure (at a dosage range below or around permissible limits), i.e., they should serve as early reversible predictors before overt health risks are impending;
- levels of the contaminant measured in exhaled air, blood, or urine must be quantitatively relatable to an adverse health effect;
- measurements of metabolites or biochemical changes resulting from the inhalation of contaminants, must also be quantitatively relatable to an adverse health effect;
- biological tests must yield information on potential health risks equal or superior to the information obtained by air sampling;
- facilities for accurate biological measurements must be readily available at costs below or not greatly exceeding costs for air sampling; mutatis mutandis, the same can be said for biological tests for non-chemical work factors.

In addition, the following criteria should be adhered to if possible:

- high validity (sensitivity, specificity), i.e., the test data should reflect the true situation under investigation;

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— with increasing exposure (intensity and/or duration) the deviation from normal of the test data should increase quickly, i.e., there should be a steep dose-effect/response curve;

— the analytical error (e.g., inter-observer variability in the case of X-ray examinations and questionnaires; analytical variability in case of laboratory analysis) and biological variability (change of parameters from day to day, seasonal effects independent of exposure) should be small in comparison with the changes in data to be expected;

— the test may often be conducted in several stages, advancing from simple procedures with less predictive validity as screening procedures, to more elaborate tests with better predictive validity, limited to the selected population.

It should be stressed that the test methods should be clearly specified and standardized; evaluation requires rigid adherence to such standardized methods, otherwise the data will not be comparable. This does not require national or international uniformity of procedure, but comparability. At present there is a great lack of data on comparability of methods applied in various occupational health studies, even within one country, let alone between various countries. In this context, the use of reference substances is suggested in order to provide a basis for comparison of the predictive validity and reliability of multiple methods, especially in cases where a new biological testing technique is being introduced and where its suitability and sensitivity for testing a certain type of action is to be checked.

In the health surveillance of “healthy” workers a difficulty is encountered that is absent or much less evident in the clinical examination of diseased subjects. In the former case one is often limited in the choice of tests and yet the deviations to be found are likely to be much less pronounced than those in sick people. The occupational physician has to take into account the inconveniences and potential health hazards of the test method, sometimes being obliged to apply less sensitive and less specific methods than in clinical practice. A lumbar puncture is not feasible in occupational health practice, neither is intra-arterial blood pressure measurement, or liver biopsy, although such methods might yield highly valid data. However, such biological samples as urine, exhaled air, and blood are generally readily available.

5.5 Variety and complexity of procedures

Whether an extensive and complex battery of tests should be used in health evaluation programmes, or only one or a few simple tests depends upon:

1. The predictive validity of the tests in regard to the specific questions asked

In order to evaluate the degree of exposure to styrene or benzene, for example, the monitoring of mandelic acid or of phenol excretion, respectively, may suffice. To explore a potential effect on cardiovascular function in older workers, one may have to apply several tests, e.g., measurement of heart rate, blood pressure, electrocardiographic tracings, various functional tests (effect of change in posture, physical work capacity); however, if one only wants to know whether the physical workload exceeds specified limits, simple counting of the heart rate may suffice. Evaluation of subjective responses (e.g., irritation of mucosae, headache, drowsiness, fatigue) requires an extensive questionnaire; but the elucidation of a symptom such as itching, may be done with a simple test.

2. The type of preventive action considered

If the investigator only wants to see whether a health risk is present in a group of workers, and particularly if he wants to exclude such a risk, he may often be able to limit himself to a simple test. If ALA excretion in the urine does not exceed 5 mg/litre in any individual, it is likely that no excessive exposure to lead has been encountered; if the heart rate does not exceed 110 beats per minute in any individual, it is likely that the physical workload is not heavy; if there are no dips in the audiogram in the range 3000-6000 Hz in any individual, it is likely that there is no permanent noise level above 90 dB (perceived).

In the periodic examination of a group of workers, exposed to a workload up to or above the permissible level, several tests may have to be applied. In cases of exposure to inorganic lead, these will include: ALA in urine and haemoglobin and lead in the blood (see Annex 1). In the case of physical workload, the heart rate, the electrocardiogram, and the blood pressure will have to be checked; in cases of noise, a speech audiogram will also be needed.

If the aim is to follow up the health of individuals, particularly in cases of potential hypersusceptibility, it may be necessary to apply a whole series of clinical methods in order to evaluate the response and the cause of the hypersusceptibility (e.g., existing diseases).
If workers are exposed to work factors, the potential health effects of which are not adequately known, a large battery of tests may have to be applied, e.g., in exposure to a new chemical agent.

If the purpose is to discover the presence of diseases that are not related to work, the entire battery of tests for standard medical practice is applicable.

3. *Evaluation of the positive aspects on health*

If the aim is to obtain information on the role of work in promoting the health of workers, the tests available are less well established; the development of such tests should be the subject of future work.

### 5.6 Simple, practical tests

The development and application of simple, practical tests to be used in the early detection of health impairment in workers is essential for the progress of occupational health. Even if complex equipment and highly trained staff are available, such simple tests will often be preferred, if they have been validated for the given purpose. Practical tests are those that (1) can be applied in the field (industry, agriculture), by peripheral occupational health services and in routine laboratories; (2) can be applied by semi-skilled, auxiliary personnel; and (3) are not expensive with regard to the cost of equipment, supply, and staff. Even if such tests do not always provide the most quantitative data, they can be very important for the identification of workers at risk; some semi-quantitative tests may even provide completely adequate information on the early phase of response.

Some examples of available practical tests are given below:

1. For exposure to *organophosphorus insecticides*, a number of field kits for the measurement of total cholinesterase activity in blood are available.

2. In exposure to *dusts and organic fibres* (e.g., wood, carbon, jute, hemp, and washing powders), early impairment can be detected by tests of ventilatory capacity (e.g., vital capacity, forced expiratory volume, peak flow rate (see Annex 3)); these tests may be supplemented by a standardized questionnaire and an X-ray examination.

3. For evaluating the hazards of *lead* exposure, simple, practical tests include the semi-quantitative test for coproporphyrin in the urine and simplified kits for determining ALA in the urine.

4. For exposure to *volatile agents*, some field kits are available for measuring the agent in exhaled air (especially alcohol and carbon monoxide); however, there is a need to develop more practical tests for exhaled air.
5. For exposures that affect the blood and haematopoiesis, one can measure haemoglobin, sedimentation rate, and total and differential leucocyte counts, all of which may be non-specific for an agent, but may indicate early impairment.

6. Analysis of urine for protein and trichloroacetic acid (Fuj iwara Test) may be of value for certain exposures such as cadmium and trichloroethylene.

Although the above examples indicate the existence of some practical tests, there is a great need for standardization even of these tests, and for the development of many more practical and simple procedures. Efforts should be made to develop practical tests geared to local needs and to specific hazardous exposures.

6. PSYCHOSOCIAL FACTORS AT WORK AND THEIR HEALTH EFFECTS

The psychosocial environment and working conditions play an increasingly important role in determining the state of health of working populations, both in industrialized and in developing countries. The problems may vary from highly industrialized countries, where automated and semi-automated processes are frequently used, to those conditions in industrializing countries, where workers are in the process of adaptation to mechanization and are undergoing a transfer adjustment to new processes and techniques.

This section is intended only to demonstrate the importance of this field, which requires special consideration of its own because it is so extensive. Brief reference will be made to the types of psychosocial stimuli in the work environment, the human factors that play a role in determining the positive and negative health effects resulting from these psychosocial stimuli, and the different types of effect resulting from exposure to these stimuli.

6.1 Psychosocial factors

These can be classified into three closely interrelated categories: (a) work organization; (b) general working conditions; and (c) type of work. Examples of factors relating to work organization and to general working conditions include: shift-work, work stability, underload, group cohesion, leadership style, security, workers' participation and communication, physical and chemical factors in the working environment, the system of
payment and holidays, conditions of employment of vulnerable groups, the size of the establishment, and welfare conditions.

Factors relating to the type of work include the performance of repetitive tasks, a high degree of responsibility, over-stimulation, under-stimulation, isolation, and other task requirements, as well as various ergonomic factors.

6.2 Human factors

These include (a) endogenous factors, such as age, sex, genetic factors, past psychological conditions, vulnerabilities, capacities, and expectations, and (b) exogenous factors, such as family life, culture, and society.

6.3 Health effects

These can be positive effects when they involve adaptation, coping, and qualification, or negative when stressors are beyond human tolerance. The effects can be classified in two main categories:

(a) Psychological and behavioural changes, including hostility, aggressiveness, anxiety and depression, tardiness, job satisfaction or the reverse, passivity, alcoholism, drug abuse.

(b) Physical or psychosomatic ill-health, including fatigue, headache, pain in the shoulders, neck and back, propensity to peptic ulcer, hypertension, heart disease, and rapid aging.

There have been controlled studies such as determination of catecholamine in urine, demonstrating biochemical changes occurring as a result of exposure to psychosocial stressors.

Occupational physicians play the key role in this field; they should be trained to deal with the above factors in places of employment; guidelines to this effect should systematically be developed.

7. AREAS IN WHICH FURTHER KNOWLEDGE IS NEEDED

There are still several areas that deserve special attention and further research in order to promote preventive health examinations at work. The following topics may be mentioned:

1. For many physicochemical work factors, adequate exposure-effect/response relationships in human beings are not known; many permissible limits are based mainly on animal data, not evaluated in epidemiological
studies. Even work factors, to which large numbers of workers are exposed in various parts of the world, have not been adequately studied in epidemiological research, particularly in regard to long-term, low-level exposures. To mention only a few examples, it is not known: whether there are any quantitative relationships between medium noise levels and presbyacusis; whether noise leads to social alienation; whether long-term exposure to solvents affects brain function; or whether cardiovascular health is impaired by exposure to carbon monoxide or to various metals.

2. Comparability of data is often poor, owing to inadequate communication and coordination between institutions; there is a need for intercomparison programmes at national and international levels, based upon reference standards. It is not necessary that this should lead to uniform methods, but to comparable data.

3. This report has emphasized the influence of host factors on the effect of work factors. Too often such data are given as if human beings of different age, sex, socioeconomic status, smoking habits, etc., have a qualitatively and quantitatively similar response. There is a great need to study the effect of various exogenous and endogenous host factors on effect/response relationships as discussed in section 4 (page 15).

4. Too little is known about the relation of reported effects on health in humans to many of the early effects that have been established either in animal experiments or in observations on humans.

5. Too little knowledge is available about the health effects of combined exposure to various biological, chemical, physical, and psychosocial factors; up to now, only very few data have been produced on synergistic responses resulting from the interaction of work-related factors and also from the interaction of these with factors not related to work.

6. The study of early effects on higher and peripheral nervous function has attracted increased attention in recent years.* The significance of such effects as possible indicators of health impairment is not yet well established.

7. Knowledge about the potential carcinogenic, mutagenic, and teratogenic effects of occupational exposure to toxic agents and certain physical work factors is very inadequate. There is a lack of data that would permit the early detection of pre-carcinogenic changes, and the health significance

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of chromosome changes observed in studies of peripheral blood has not
been sufficiently established.

8. There is not nearly enough knowledge about the long-term effects of
underload as discussed in section 2.

9. There is a dearth of information about the biochemical changes caused
by psychosocial and ergonomic work factors and about quantitative methods
for the identification of resulting early health impairment (see page 10).

7.1 Criteria of priority in selecting study areas

One of the terms of reference of the Study Group, was to prepare a list
of priorities of exposure—health effects for future work by WHO, emphasiz-
ing the early detection of health impairment (see also Annex 2).

The following criteria for determining priority were agreed upon:

1. The number of workers exposed, the hazard of exposure, and the
   number of countries involved.

2. Seriousness of effects in regard to health impairment: death; per-
   manent incapacity; reversible incapacity; effects such as pain and dis-
   comfort.

3. Relevance for community health, e.g., in regard to long-term, low-
   level exposure to chemical agents and certain physical factors, and in regard
to early detection of degenerative and communicable diseases.

4. Special types of response: effects on various biological systems that
   appear to be relevant to the causation of widely prevalent diseases. Such
   studies may reveal hitherto unknown pathophysiological mechanisms that
   may further the progress of medical science.

5. New evidence of effects, previously unrecognized, if suggestive
   exposure conditions are more or less universal.

6. Introduction of new chemical substances and new technologies on a
   large scale.

8. ILLUSTRATIVE EXAMPLES OF EARLY DETECTION
   OF HEALTH IMPAIRMENT

8.1 Introduction

In the preceding sections, general principles have been presented for
describing health impairment, population characteristics, and methodology
for occupational health evaluation. The Group agreed that it was important
To illustrate some of these general principles with a few examples. Two approaches are used: the first involves the study of physiological functions, organ systems, and biochemical parameters; the second involves the early detection of health impairment caused by chemical and physical factors.

The first approach is illustrated by (a) the use of lung function tests for the early detection of occupational respiratory impairment; and (b) the use of biochemical parameters for occupational health evaluation. The second approach is illustrated by studies of the early health changes in exposure to chemical agents (e.g., carbon disulfide, lead, and insecticides) and physical stress (using noise as an example).

The two approaches overlap to some extent, particularly with regard to changes in biochemical parameters resulting from exposure to chemical agents. In some cases, there will not be a clear line of demarcation between biological changes that are primarily indicators of exposure and those that relate directly to health impairment.

Examples of the different approaches are presented below. The biochemical parameters discussed include enzymes, non-enzymatic proteins, and other biochemical substances, with special emphasis on their use in evaluating liver and kidney function and their relative specificity for certain changes. The section on detection of respiratory impairment provides a description of some substances known to have such an adverse effect and methodology for measuring ventilatory capacity. The effects of exposure to carbon disulfide are presented according to the previously described categories of criteria of health impairment, while the effects of inorganic lead and of organophosphorus and organochlorine insecticides are described primarily as specific changes in biochemical parameters measured in biological fluids. Noise, as one example of a physical stress on workers, is presented in terms of its overall effects and general aspects of audiometric testing, with emphasis on the difficulty of early detection of hearing loss before some irreversible damage has occurred.

It is expected that WHO will eventually undertake more comprehensive evaluation of criteria for detecting early health impairment as indicated by changes in various organ systems following exposure to different occupational hazards. Attention should be paid to relatively simple methods that do not make great demands upon financial and manpower resources.

8.2 Early detection of occupational respiratory impairment

The aims of early detection of respiratory impairment are: first, to detect susceptible workers and remove them from exposure before they suffer any permanent incapacitation; secondly, to provide knowledge on the natural history of respiratory disease that is essential for its management.
in the early stages; and thirdly, to identify the nature of hazardous exposures and, in combination with environmental studies, provide data for establishing exposure/effect relationships.

Examples of occupational exposures causing respiratory impairment

The following examples are not intended to be comprehensive. They cite some of the commonly encountered respiratory diseases resulting from occupational exposure.

(a) Mineral fibrogenic dusts

An example of this is free silicon dioxide. In the early stages of silicosis there is usually no impairment of any parameter of lung function. With more advanced disease, impairment of total lung capacity (TLC) is commonly present. Vital capacity (VC), residual volume (RV), forced expiratory volume (FEV), and functional residual capacity (FRC) are all useful criteria (see section 8.3). There may also be a slight reduction in gas transfer, as in pneumoconiosis in coal workers. Lung function tests appear, on present evidence, to have no specific value in the early detection of respiratory impairment. However, some of the early manifestations of silicosis could be symptomatic: irritant cough, dyspnoea on exertion, and early radiographic signs that may not be related to functional changes.

(b) Vegetable dusts

These include a wide variety of dusts commonly encountered in the agricultural and textile industries, in food processing, and in woodworking. One of the prevailing occupational respiratory diseases in exposure to these dusts is obstructive lung disease.

Respiratory function tests are among the most valuable tools in the early detection of such diseases. In addition, there are such specific symptoms as "Monday tightness" in byssinosis and other more general respiratory symptoms, mainly cough. Here determination of the FEV₁,₀, taken in conjunction with the replies to standard questionnaires, gives adequate indication of early respiratory impairment. There are also studies on the use of patch tests in the early detection of respiratory disease resulting from exposure to wood dust.

(c) Chemical agents

Chemical agents may produce acute respiratory irritation at different levels. These acute conditions are outside the scope of this report. Other chemical substances, e.g., beryllium, give rise to complex respiratory symptoms. The Group agreed, however, to cite the example of exposure to diisocyanatotoluene (TDI) in view of the possible evaluation of its early
effects by lung function studies. In the surveillance of workers exposed to TDI, the recommended lung function test is the forced expiratory volume (FEV). It would also be advisable to measure the forced vital capacity (FVC). Over long periods of employment, a 6-monthly interval between examinations is recommended. As a significant proportion of workers who become sensitized to isocyanates will probably develop symptoms within 6 weeks of engagement, there is a need for more frequent tests in the early weeks and months of employment.

(d) Biological agents

It has been noted that among workers engaged in the production of food concentrates and of drugs of biological origin respiratory impairment readily occurs. A problem of increasing magnitude is respiratory impairment in workers exposed to enzyme washing powders; the recommended lung function tests are FEV₁₀ and FVC. They are used in conjunction with a questionnaire on respiratory symptoms, history taking with particular reference to atopy, clinical examination, chest X-ray, and skin testing by the prick method using an enzyme reagent and common allergens.

8.2.1 Use of lung function tests

These tests are often used to detect early impairment of respiratory function. There are many such tests that can be used to evaluate the type and magnitude of impairment, but it has been found that the measurement of ventilatory capacity is the most appropriate, simple, and feasible. It is used in field studies and in the routine daily work of occupational medical units.

The determination of forced expiratory volume (FEV) and of forced vital capacity (FVC) are particularly useful for the early detection of respiratory impairment. The results should be evaluated by reference to tables of normal values according to age, height, race, and sex. The timed forced expiratory volume (FEV₁₀) is the volume of air that can be expelled in 1 second with maximum effort after filling the lungs completely. The FVC is the maximum volume of air that can be expelled with maximum effort after a full inspiration. The FEV₁₀ depends on the volume available for expulsion (which should be the VC) and the rate at which it can be expelled, and is therefore a simple test of overall ventilatory efficiency. Weakness of the expiratory muscles from pain, paralysis, or debility will reduce the FEV₁₀, but, after the first 200 ml, it is less dependent on effort than might be expected because, even in normal persons, maximum effort tends to narrow the airways and counters the effect of increased expiratory pressure. In most studies of ventilatory capacity, standardized questionnaires on
respiratory symptoms are used. Pre-employment values are important and are used in the evaluation of early changes.

8.2.2 Closing volume test

The closing volume test is a recently introduced method that is simple to perform and simple in concept, although the mechanism does not appear to be fully understood. The subject exhales to residual volume (Phase I) and then slowly inhales (Phase II). The first portion of the inspirate contains a bolus of marker gas (either helium or radioactive xenon), which is distributed preferentially to the apices of the lung. The subject continues to inhale to total lung capacity, and he then slowly exhales to residual volume. The concentration of marker gas is found to remain low and to vary only slowly during most of the expiration (Phase III) but when a certain point is reached there is an abrupt increase in concentration (Phase IV), which corresponds to the "closing volume" at which flow from the dependent regions of the lung ceases. This may, or may not, determine the residual volume of the lower regions. Flow continues from the apical regions until the residual volume of the lung is reached.

It is suggested that the volume at which closure takes place during expiration is larger in the presence of early airway abnormality. Results show that most people under twenty do not have a phase IV; that some adults have a constantly rising phase III and no phase IV, and that others may have a phase IV one day, but not the next. This suggests that the phases of the process may be more complex than at first appears and at the moment comparative studies on this test are being undertaken in different institutes. Until the results of further research are known, the technique must remain of limited utility outside the laboratory.

8.3 Biochemical parameters for occupational health evaluation

8.3.1 Introduction

Changes in biochemical parameters as measured in various biological fluids may often be among the more sensitive indicators of early changes in health due to hazardous agents in the work environment. Such changes represent a reaction to the exposure to the hazardous agent and may, in some cases, indicate an actual effect on health. In other cases, they may only indicate homoeostatic and compensatory mechanisms, which are reversible. In still other cases they may indicate minor cellular damage for

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which regenerative processes are sufficient to preclude health impairment. Thus, quantitative evaluation of biochemical parameters and the establishment of dose–effect/response relationships are essential.

Advances in analytical technology have made it possible to identify and quantify numerous biochemical parameters that were previously unrecognized. Many of these parameters are still only of value in research studies—some because they require complex instrumentation, others because the significance of the observed changes has not been established. Thus, in the choice of specific biochemical parameters their predictive validity as regards exposure and impending or actual health impairment is an important criterion. Only a few have a well-established predictive validity; some only have value when used in adequately designed epidemiological studies. Automatic analysis with microtechniques has not only promoted the measurement of multiple components but has also helped to provide a profile that may be important in health evaluation.

Since cells and tissues generally respond in a limited number of ways to a wide variety of different stresses, the changes observed are often not specific. At times the quantitative nature of the change provides somewhat greater specificity, but in most cases an independent means of establishing exposure to a particular agent will be a prerequisite for confirming a cause–effect relationship. In a specific work environment with an established exposure to one or more hazardous agents, certain biochemical parameters may be considered as specific for practical purposes. This is particularly true when the pre-exposure values for the biochemical parameters have been determined. Non-specific tests may have particular utility in that they show the integrative effect of exposures to combinations of hazardous agents and stresses.

It will be possible to give only a few examples of some biochemical parameters with well-established significance and some that are rather esoteric or require further research.

8.3.2 Changes in enzymatic activity

Increased enzyme activity in plasma or serum may indicate lesions of specific organs, e.g., the liver, or of specific tissues, e.g., release of intracellular enzymes into extracellular space as evidence of muscle involvement. It may at times be possible to detect early changes related to membrane permeability by the presence of enzymes predominantly present in the cytoplasm of cells (C-enzymes) before more extensive cell damage causes the liberation of enzymes bound to intracellular structures, such as mitochondria (M-enzymes).
In other cases, the enzyme activity may be related to ubiquitous metabolic activities that are not specific for any organ or tissue, e.g., enzymes involved in glycolysis, the pentose-phosphate-cycle, and amino acid metabolism. In still other cases, enzyme activity may decrease (enzyme inhibition) owing to direct action of a toxic agent on the active part of an enzyme, e.g., cholinesterase activity in erythrocytes and plasma after exposure to organophosphorus insecticides, or delta-aminolevulinic acid dehydratase activity after erythrocyte exposure to lead.

When exposure to a specific toxic agent has been recognized, and when it is known that the toxic agent will primarily affect a specific organ or tissue, then certain enzyme activities may become specific for practical purposes. The field of enzyme diagnosis has been broadened by the investigation of iso-enzymes. These fractional parts of the total enzyme activity may be identified by electrophoresis and chromatography, thus permitting a significant increase in organ specificity. Lactate dehydrogenase (LDH) may be separated into five iso-enzymes, LDH1, LDH2, etc., which occur mainly in the heart muscle, kidney, and liver. Hepatotoxic agents will particularly increase serum LDH1; kidney disease LDH2, LDH3 and LDH4. Iso-enzymes have also been detected for serum glutamic oxaloacetic acid transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), creatine phosphokinase (CPK), and alkaline phosphatase. This opens up the possibility of refinement in diagnosis of early biological responses, with a higher predictive validity (sensitivity, specificity) than if total serum enzyme activity is measured.

In the last decade, the phenomenon of enzyme induction has been recognized; the toxic agent induces the endoplasmic reticulum (mainly of the liver) to produce more enzymes. This response may be regarded as a defence mechanism, although the resulting metabolite may prove to be more toxic than the original chemical. Because induction of some enzymes may be due to a variety of chemicals, the phenomenon is often not specific for the agent considered. This may explain, for example, the interference of drugs with the response to occupational chemicals, and vice versa. It is not necessary to measure enzyme levels themselves, but merely the consequence of the increased activity on the pharmacokinetics of non-hazardous agents. This procedure opens up new possibilities for the early detection of exposures to certain organochlorine compounds.

8.3.3 Enzymatic changes and liver function

Disturbances of liver function may be indicated in some cases by changes in the plasma level of γ-glutamyltransferase, ornithine carbamoyl-transferase, L-iditol dehydrogenase (sorbitol dehydrogenase), alcohol dehydro-
Enzymatic changes and kidney function

When a kidney is damaged, cellular enzymes are released into the tubular lumen and their determination in urine may provide a useful index of kidney damage. Furthermore, since enzymes may be located in specific sites (glomerular tubule) or in specific cell compartments (mitochondrion, lysosome, etc.) it would theoretically be possible to determine the primary site of the cellular lesion from a comparison of the relative rates with which various enzymes appear in the urine following kidney damage. If glomerular permeability is increased at the same time as tubular reabsorption is altered, increased quantities of serum enzymes might also be detected in the urine. The output of urinary enzymes reflects the anatomic integrity of the kidney and because the kidney has a large functional reserve capacity changes in urinary enzyme excretion should precede any change in physiological function. The measurement of enzyme excretion in the urine is in fact a more sensitive and an earlier means of detection of kidney damage than the commonly used functional tests, such as clearances of specific substances or the blood level of certain excretory products.

Up to now, however, urinary enzyme determination has not been very useful for the differential diagnosis of human kidney disease. Nevertheless, measurement of enzyme activities in urine can help as a screening method for the early detection of kidney injury in persons exposed to nephrotoxic chemicals.6

The kidney is a particularly rich source of alkaline phosphatase and the highest activity is found in the brush border of the epithelial cells lining the convoluted tubules. In human urine, alkaline phosphatase activity is regularly present; this normal urine enzyme is different from that found in serum and is therefore unlikely to arise from that source. Indeed, normal urine levels of alkaline phosphatase are found in man even when the serum activity is high. All toxic exposure accompanied either by necrosis of renal tubular cells or disturbances of glomerular filtration provoke increased alkaline phosphatase activity in the urine.8 Since alkaline phosphatase

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from serum or kidney can be separated by electrophoresis, it might perhaps be possible to localize the site of the lesions (glomerular or tubular) by finding out which alkaline phosphatase is mainly increased.

In human urine, acid phosphatase activity is also regularly present. In women, acid phosphatase of the urine is derived exclusively from the kidney, whereas in men prostatic secretion contributes significantly to urinary levels of this enzyme. Since in the kidney the highest specific activity of acid phosphatase is found in the glomeruli, an increased urinary concentration of this enzyme (in women and children or in ureteral urine samples in man) can indicate an active glomerular lesion.

β-N-acetylglucosaminidase, glycine amidinotransferase (arginine-ornithine transaminase), and α-glucosidase are not found in serum, but it has been shown that their concentration in the urine increases after toxic renal damage.

Human observations or animal experimentation have demonstrated that the activities of β-galactosidase, β-glucosidase, lactate dehydrogenase, and aspartate aminotransferase increase after exposure to nephrotoxic agents. The study of the urinary excretion of β-glucosidase and β-galactosidase may also be of value in assessing the presence and extent of kidney damage, mostly at the tubular sites.

Increased aminopeptidase activity in the urine can be found in various pathological conditions of the kidneys, particularly in the case of tubular lesions induced by various chemicals, such as mercury salts. The highest values are encountered when the noxious substance affects the proximal part of the tubules, which contains high activities of aminopeptidase.

It is known that an increase in lysozymuria and ribonucleasuria indicates tubular damage. Thus, in workers exposed to cadmium, determinations of urinary lysozyme and ribonuclease activity aid in the early diagnosis of cadmium nephropathy.*

8.3.5 Enzymatic changes and other physiological systems

In subjects exposed to carbon disulfide, indirect evidence exists that there is a loss of drug-processing enzymes; in workers exposed to lead, decreased activity of Na+K+ATPase in the erythrocyte membranes has recently been observed, particularly in highly exposed workers, also suggestive of relatively high ambient exposure. The presence of aminopeptidase in peripheral leucocytes is of very high validity as an indicator of exposure to trichloroethylene.

A very extensive literature survey on the significance of measurements of enzyme activity in occupational health programmes has been made by Muster.¹

8.3.6 Changes in non-enzymatic proteins

A distinction is made between changes in serum protein concentrations and in serum protein pattern. Specificity is generally rather low, but sensitivity may be high.

Classical precipitation reactions, e.g., the zinc sulfate precipitation test and thymol turbidity tests, are based respectively upon changes in immunoglobulin concentrations and in β-lipoprotein concentrations.

Electrophoresis is the method used for examining the protein pattern, i.e., the relative contribution of various proteins to the total serum protein. Special techniques have been developed for increasing the possibility of separation of various proteins and discriminating between components. Normal routine electrophoresis distinguishes between albumin, α₁-globulin, α₂-globulin, β-globulin and immunoglobulin; the relative concentrations can be measured. A more refined technique is polyacrylamide-gel electrophoresis (PAGE): instead of 5-6 components this distinguishes 15-20 different components, thus increasing the possibility of observing early changes in composition. At the moment, however, it is still difficult to assess the health significance of the changes observed with the highly complex PAGE method.

A few examples of protein changes due to toxic exposure may be given:

- carbon monoxide in a concentration of 115 mg/m³ for 20 min induced an increase in α₁-globulin and a decrease in immunoglobulin;
- an increase in β-lipoprotein and a slight decrease in α-lipoprotein have been observed in workers exposed to carbon disulfide;
- in workers exposed to trichloroethylene, β-globulin was increased; in subjects exposed to benzene, hypoalbuminaemia and an increase in β-globulin and immunoglobulin have been observed;
- in several groups of workers exposed to a mixture of pesticides, an increase in α-globulin was seen, even after moderate exposure, as the most sensitive change in the serum protein pattern.

It should be stressed once more that toxic agents constitute only one group of factors determining the serum protein pattern and concentration.

However, the variability (increase, decrease) in biochemical levels may provide an early, reversible indicator of such exposure, if the data are compared with those in adequate controls.

Immunoelectrophoresis is another refinement of electrophoresis: the protein fractions are exposed to specific antisera, with which they combine to form precipitates. This enables many more subfractions to be diagnosed: it is possible to distinguish various glycoproteins, pre-albumins, immunoglobulins, haptoglobulins, and haemopexins. The application of this method in industrial toxicology is still limited as it demands specialized laboratories. Immunoelectrophoresis can also be used to evaluate the immunochemical effect of toxic agents, such as silicon dioxide, zinc oxide, or isocyanates, which induce the formation of antigens in the body.

The glomerular capillary membrane has the particular property of being relatively impermeable to large molecules. Proteins with a molecular weight above 40,000 will not normally traverse the barrier easily. Proteins of smaller size penetrate the glomerular capillary membrane more easily, but their appearance in the urine is limited by subsequent tubular reabsorption.

In cases of intoxication in which glomerular permeability is increased, larger quantities of high molecular weight proteins (albumin, transferrin, etc.) enter the glomerular filtrate and ultimately appear in the urine, but the urinary concentration of low molecular weight protein is not increased. When increased proteinuria is a consequence of tubular dysfunction, the amount of protein filtered by the glomeruli is not increased and the low molecular weight proteins, together with the small quantity of high molecular weight proteins that are normally filtered, appear in larger quantities in the urine because tubular reabsorption is incomplete. However, by comparison with normal urine, the proportion of low molecular weight protein (α₂-microglobulin, β₂-microglobulin) is greater than that of high molecular weight proteins because the latter do not filter easily. When both sites—glomeruli and tubules—are altered, the proteinuria consists of a mixture of low and high molecular weight proteins.

Representatives of these two types of protein (high molecular weight: albumin, transferrin, etc.; low molecular weight: α₂-microglobulin, β₂-microglobulin, lysozyme, ribonuclease, etc.) can be measured by immunochemical, electrophoretic, or enzymological methods and their determination may thus be useful for the detection of toxic kidney damage. Chronic exposure to inorganic mercury, intoxication by potassium perchlorate, sodium chlorate, and the chelating agents penicillamine and ethylenediamine tetraacetate may induce an increased glomerular permeability (nephrotic syndrome) with an increase in the concentration of high molecular weight proteins in the urine. Acute intoxication by inorganic mercury, ethyleneglycol, halogenated solvents, prolonged excessive exposure to lead,
cadmium, and uranium may induce tubular damage, with a preferential
increase in the concentration of low molecular weight proteins in the urine.

Cadmium proteinuria has received much attention because proteinuria
is the most characteristic feature related to the nephrotoxic action of the
metal.*

Proteinuria may occur in the absence of any obvious effect on health and
is roughly correlated with the duration of exposure. For example, during a
recent survey, it was found that in a group of workers exposed to cadmium
dust for less than 20 years the prevalence of excessive proteinuria was
15%, and in a group exposed for more than 20 years (on the average
27 years) the prevalence of proteinuria was 64%.* Since cadmium pro-
duces damage to the tubules, it is evident that in the classical form of
chronic cadmium poisoning the protein pattern obtained by electrophore-
sis separation of urinary protein will show an increased excretion of low
molecular weight proteins, such as α₂-microglobulin, and β₂-microglobulin,
as well as a slight increase in the excretion of high molecular weight pro-
teins, such as albumin. As indicated previously, the low molecular weight
enzymes (lysozyme and ribonuclease) are also excreted in greater quantity.
Tubular lesions due to cadmium poisoning may also be associated with
an increased aminoaciduria. Some recent evidence indicates, however, that
in the early phase of cadmium-induced kidney lesions the clearance of
high molecular weight proteins (albumin) may be increased first; this suggests
either an enhanced glomerular permeability or a specific alteration in the
mechanism of tubular reabsorption of high molecular weight proteins.*

Excessive proteinuria has been observed in workers exposed to concen-
trations of cadmium dust below the American threshold level value
(TLV), and proteinuria proved to be a more sensitive indicator than changes
in lung function. Glomerular proteinuria appears to be an earlier sign than
mixed (glomerular + tubular) proteinuria; the proteinuria probably does
not occur if the cadmium excretion in the urine does not exceed 15 μg/g of
creatinine.

8.3.7 Changes in other biochemical parameters

Neurohumoral reactions

Some agents may affect the function of the endocrine system by stimu-
lation of the nervous system. In the brain, the enzyme monoamine oxidase

* FREIBERG, L., PISCATOR, M. & NORDBORG, G. F. Cadmium in the environment:
an epidemiological and toxicological appraisal, Cleveland, Chemical Rubber Co., 1972.
* ROELS, H. A., LAUZERTS, R. R. & BUCHEI, J. P., Study on cadmium proteinuria,
  glomerular dysfunction : an early sign of renal impairment, Paper presented at an Inter-
national Symposium on Recent Advances in the Assessment of the Health Effects of
(MAO) prevents the excretion of epinephrine and catecholamines from the suprarenal glands; in thyroid hyperfunction MAO-activity is low; the reverse is true in thyroid hypofunction. Inhibition of MAO may be found following exposure to mercury, carbon disulfide, and tetraethyl lead; measuring the uptake of $^{39}$I by the thyroid may serve as an early biological test.

**Glutathion**

The erythrocyte membrane is continuously exposed to oxygen; reduced glutathion (GSR) aids in maintaining the membrane by combating oxidation. Haemolytic agents, e.g., arsine, oxidize sulfhydryl (—SH) groups in enzymes; a high GSR content may counteract the oxidative power and so protect the integrity of the membrane. A reduced GSR content promotes haemolysis. According to some authors, exposure to inorganic lead may decrease the GSR content of the erythrocytes as a very early indicator.

In some ethnic groups, a deficiency of glucose-6-phosphate dehydrogenase occurs as a genetic trait; such subjects are liable to haemolysis if exposed to benzene, lead, or aromatic amines, because such exposure leads to a decrease in reduced glutathion. A pre-employment test has been devised to detect this type of hypersusceptibility.

**Cholesterol**

An increase in cholesterol has been found in workers exposed to carbon disulfide and maybe also to chlorinated hydrocarbon insecticides; decrease has been observed in subjects exposed to vanadium pentoxide and to other vanadium compounds.

**Neuraminic acid**

Exposure to cobalt, even in low concentrations, produces an increase in serum neuraminic acid.

**Aminoaciduria**

Following exposure to cadmium, an increased excretion of threonine and serine and, in case of acute lead intoxication, a decrease in creatinine excretion have been observed. In a group of workers exposed to pesticides, aminoaciduria has been found together with increased alkaline phosphatase and SGOT in serum. Aminoaciduria has also been reported in asymptomatic lead workers and in children suffering from overexposure to lead. This sign might provide an early indicator of nonspecific functional injury to proximal renal tubular cells.
Porphyrin metabolism

Exposure to inorganic lead is particularly likely to result in various early indicators of changed porphyrin synthesis (see under lead); one should be aware of the effect of alcohol as another cause of coproporphyrinuria.

Bile pigments

Serum bilirubin is increased in disturbed liver function and in increased haemolysis following exposure to typical liver poisons, such as carbon tetrachloride, chloroform, and phosphorus, and haemolytical agents, such as arsenic, particularly in the case of acute intoxication. Hyperbilirubinaemia cannot be regarded as an early sensitive indicator.

8.3.8 Conclusions

This short review can serve only to give some indications of the possible uses of various biochemical parameters in the early evaluation of impending or actual health impairment. Specificity is often rather low, but sensitivity may be high; a rigid epidemiological design is needed to evaluate the role played by toxic exposure, in distinction to many other possible causative conditions.

A change in a biochemical parameter does not necessarily indicate an adverse effect; the relevance to health should be established.

Modern automatic laboratory analysis can greatly promote the standardization of blood examinations; particularly if several parameters are examined at the same time, the examination of the biochemical profile may provide an important tool in health monitoring.

On the whole, biochemical tests are proving to be very promising aids in the early detection of health impairment due to occupational factors, but much further research is needed to increase knowledge of biochemical parameters and to make biochemical methods accessible to the occupational health services.

8.4 Early detection of health impairment due to carbon disulfide

8.4.1 Introduction

Most of the early manifestations of poisoning due to carbon disulfide are highly non-specific. In carefully conducted studies, these early non-specific changes, or their combinations, may be diagnostically specific if, and only if, they have been shown to be causally related to exposure to carbon disulfide. Furthermore, the excess occurrence of causal manifesta-
tions among exposed groups should be quantified and their relative importance as criteria for diagnosing changes that are precursors to carbon disulfide intoxication should be established. This may be accomplished at a group level, but for changes in individuals it will usually be possible to determine only the probability of carbon disulfide intoxication.

8.4.2 Changes in chemical, biochemical, and morphological parameters

Disturbances in lipid metabolism have long been linked with exposure to carbon disulfide. The serum cholesterol level has been found to be elevated in some studies and normal in others. These conflicting results may be explained by different exposure levels in different studies. The clearing factor (lipoprotein-lipase) activity is lowered and the β-lipoprotein fraction may be elevated in exposed workers. However, there are no studies convincingly showing the diagnostic value of any of the blood lipids because of their high degree of non-specificity. It was reported by one member of the Group that changes in blood coagulation have been found after carbon disulfide exposure.

All these changes have been found in exposed groups compared with controls. Such changes are of limited value, however, for early diagnosis in an individual case.

8.4.3 Changes in functions of systems

Effects on the nervous system

Neurological signs. Neurological abnormalities detectable at a physical examination, such as lesions of cranial nerves, extrapyramidal involvement, polyneuritis, and dysfunctions of the autonomous nervous system, are among the most outstanding clinical manifestations of carbon disulfide poisoning. To what extent they occur in the subclinical stage is largely a matter of definition. One can only tentatively postulate that mild forms of the signs listed above may start appearing early in the course of exposure, and that their frequency and severity increase as the disease advances.

Neurophysiologic signs of effects on the peripheral nervous system. Electromyography (EMG) and measurement of motor conduction velocities of peripheral nerves have proved to be sensitive methods for detecting early nervous system damage, even in neurologically normal workers exposed to carbon disulfide. The EMG abnormality most often found consists of a diminished number of motor units at maximum contraction. Other common

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findings are fibrillations and increase in the duration of motor unit potentials. The maximum motor conduction velocities (MVC) are slowed, especially in the leg nerves, and the distal latencies are prolonged. However, the most sensitive test for peripheral nervous involvement appears to be the conduction velocity of the slower fibres (CVSF) of the ulnar and deep peroneal nerves. In a recent epidemiological study comprising 118 male workers in a viscose rayon factory and 100 controls from a paper mill, the most important findings were as follows: The conduction velocities in the nerves of the exposed men were generally slower than those of the controls. The most distinct differences (all P-values < 0.01) were obtained for the CVSF of the ulnar and deep peroneal nerves, the MCV of the deep peroneal and posterior tibial nerves, and the motor distal latency of both the median and ulnar nerves. As much as 48% of the exposed men, as compared with 24% of the unexposed men, had polyneuropathy, here defined as "pathologically" reduced conduction velocities in two or more nerves; 28% and 20%, respectively, were borderline cases, and 24% of the exposed and 56% of the non-exposed men were completely free from neuropathy. The exposed group in this study was composed predominantly of clinically "well" men exposed for several years (median 15) to concentrations of carbon disulfide + hydrogen sulfide, the carbon disulfide concentrations having been 60–120 mg/m³ in the 1950s, 30–90 mg/m³ in the 1960s, and mostly below 60 mg/m³ during the last years. Little more than half of the men were still exposed at the time of examination; the rest were working in "clean" departments.

Besides illustrating the usefulness of electrophysiological methods for the early detection of effects of carbon disulfide, this study also demonstrates how the specificity of a method decreases with increasing sensitivity; although there was a great excess of pathological findings in the exposed group, as many as 24% of the controls were classified as having polyneuropathy.

Central nervous system — electroencephalography. In a recent study 21 abnormal ECGs were found in an exposed group comprising 54 viscose rayon workers, as compared with only 6 in a control group of 50 paper mill workers. The abnormalities consisted of slight, diffuse slow-wave abnormalities, and even spike-and-wave discharges in 3 exposed men. Thus, mild brain dysfunctions were clearly more prevalent in the exposed group in this well-controlled study.

Mental effects (psychiatric and psychological). Using a standardized battery of tests, it has been possible to obtain quantifiable measures of

various psychological functions. This renders statistical treatment of the findings possible. The test battery has been developed to measure vigilance, dexterity, visual retention, motor speed, coordination of eye and hand, intelligence, basic perception and conceptual abilities, disturbed idealization, and control of hand movements.\(^a\)

Using these tests, it was possible to discriminate between patients with carbon disulfide poisoning, exposed but seemingly healthy viscose rayon workers, and unexposed controls. The exposed but seemingly healthy group came closer to the poisoned one than to the controls, thereby indicating the presence of psychological disturbances in otherwise ostensibly healthy workers (who, it should be stressed, were not examined using other sensitive methods, such as the neurophysiological ones referred to above).

In a more recent study, the application of the same type of tests showed that the most distinct difference was for retardation of psychomotor speed; 40% of the exposed and 25% of the control group showed “poor” performance, defined according to specific criteria.\(^b\) These results show a clear group difference; however, the test battery has a low specificity for carbon disulfide, as can be seen from the high number of “false positives”. It is only in combination with other methods of examination that these tests can be employed for individual diagnosis.

Psychiatric symptoms, such as irritability and emotional instability, have for a long time been accepted as early signs of carbon disulfide intoxication.

In more serious cases of intoxication, signs of psychoses, sometimes acute, may appear, together with psycho-organic symptoms. In cases with psycho-organic symptoms it is very difficult to differentiate these primary effects from those secondary to cerebral vascular lesions that may be caused by atherosclerosis, related to exposure to carbon disulfide.

**Neuro-ophthalmological effects.** In one study, the group with the mildest symptoms of carbon disulfide intoxication showed a high frequency (about 30%) of abnormal corneal and pupillary reflexes.\(^c\) Enlargement of the blind spot and narrowing of the visual field have also been reported, but it is questionable whether these signs can be regarded as early effects.

**Effects on the cardiovascular system**

The old clinical observations that led to the suspicion that carbon disulfide is an atherosclerosis-promoting agent have been corroborated by

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epidemiological studies during the last few years. For methodological reasons, the coronary arteries and those of the ocular fundus have proved the most rewarding to study, and most of the results available concern these vessels. This should not preclude the high probability of early changes of a similar type in other parts of the vascular system, mainly the cerebral vessels and the arteries of the lower extremities.

Coronary arteries. Studies in Great Britain, Norway, and Finland have clearly demonstrated that carbon disulphide must be regarded as causing excess coronary mortality.\(^8\)

In a recent five-year follow-up of one cohort of viscose rayon workers and another of unexposed paper mill workers, the relative risk for fatal myocardial infarction was 4.8.\(^8\) Both cohorts comprised 343 age-matched men at the beginning of the follow-up. In the same study, the relative risk for typical angina at the end of the follow-up was 2.8 (\(P = 0.001\)), and that of typical + probable + possible angina 2.2 (\(P = 0.0002\)).

It has been shown that cardiovascular diseases are more common among people exposed to carbon disulphide. The relative risk for “coronary” ECG findings was 1.4 (\(P < 0.05\)). However, some other studies have shown a more distinct excess of “coronary” ECGs. It is possible that dose-dependent, methodological, and even geographical factors may explain the discrepancies reported so far.

Microcirculation of the ocular fundus. Retinal microaneurysms have been found in a high proportion of Japanese viscose rayon workers, but these results were not confirmed in a recent Finnish study.\(^6\)

In this study, a high frequency of delayed peripapillary filling was found in 68 exposed and 38 non-exposed men. The calibres of the retinal arteries were significantly wider in the exposed group, a somewhat surprising finding, but one consistent with the suggestion that haemodynamic changes are responsible for the delayed peripapillary filling. Oculovolumetry (OSG) performed on 40 exposed and 40 non-exposed workers indicated a difference in the ocular pulse wave, implying differences between the groups in the elasticity of the bulbar arteries.

In conclusion, these findings suggest that studying the microcirculation of the ocular fundus by fluoroangiography and OSG definitely aids the


\(^6\) Raftta, C. & Tolonen, M. In preparation.
detection of vascular lesions related to carbon disulfide exposure, especially since the vessels can be observed directly in their natural state.

_Cerebral circulation._ Clinical observations have certified beyond doubt the involvement of the cerebral arteries in atherosclerosis induced or accelerated by exposure to carbon disulfide, and several of the neurological and psychiatric findings typical of advanced poisoning are certainly due to this mechanism. There are no specific and valid methods suitable for epidemiological research in the field that could help elucidate directly at what stage such processes begin; consequently, such studies of the subclinical stage are lacking.

_Peripheral circulation._ Most of what has been stated for cerebral circulation applies to peripheral circulation as well. However, in both instances it is important to realize the distinction between epidemiological studies and the examination of individuals with suspected poisoning. Arteriographies, isotope examinations, and similar procedures are not readily applicable in epidemiological studies, but they may still be quite informative about the state of the vascular system of individual patients. However, the lack of epidemiological experience renders it hard to quantify a positive finding in an individual in terms of the probability of a causal connexion with exposure to carbon disulfide.

_Effects on the endocrine system_

Impairment of the function of the thyroid gland,\(^a\) of the gonads,\(^b\) and of the adrenocortical system has been found in exposed groups. It is too early, however, to decide on the usefulness of these findings for early diagnosis in individual cases.

_Subjective symptoms and complaints_

Several complaints are considered to be common in carbon disulfide poisoning: irritability, insomnia, rapid mood changes, nightmares, impotence, increased sweating, general fatigue and muscular weakness, numbness, paraesthesia and pain in the limbs, headache, and subjective memory impairment. However, no clear trend emerges as to the order of appearance of the various symptoms, or to what extent they can be regarded as early effects.


In most studies, frank signs of clinical poisoning have occurred con-
comitantly, at least in some patients. For example, in a study performed
on 36 men with past or current slight to moderate poisoning, the most distinct
differences as compared with a control group of 188 men consisted of
insomnia (relative risk, 6.1), headache (6.0), paraesthesia (3.5), and general
fatigue (2.7), whereas the differences for other complaints were less marked.\* 
Although many of the men had clinical poisoning, this order of frequency
suggests that the 4 symptoms listed should be given special attention as
warning signs of incipient poisoning. However, the methods available for
obtaining data on subjective sensations are of low validity.

*Integrative changes (individual diagnosis)*

In assessing the results reviewed in the preceding section, it should be
remembered that all the effects observed are non-specific, that some require
examinations that are complicated, need expensive equipment, or are liable
to methodological errors, and that other methods, although potentially
useful, have not yet undergone enough systematic evaluation.

Taking all this into account, the following methods of examination can
be considered; interview (including neurological, psychiatric, and cardio-
vascular symptoms), physical examination, EMG and nerve conduction
velocities, EEG, psychological testing, ECG, retinal fluorescein angiography,
and blood analysis, especially determination of lipids (cholesterol, β-lipo-
protein, and clearing factor or lipoprotein-lipase). In selected cases and
to permit differential diagnosis, cerebral or peripheral angiographies may
be added to this list. Hormone determinations, especially of free thyroxin
and urinary testosterone, may prove valuable in the future, but are so far
not studied enough. Most of these methods may be carried out at an
industrial health service with special equipment.

Measurement of nerve conduction velocity and electromyography are
of such importance that the factory health service must be required to make
arrangements for carrying out these examinations, either at the factory
itself or at some nearby hospital or health centre with proper equipment.

Since all isolated effects are non-specific, the individual diagnosis becomes
a matter of probability, based on (1) a combination of findings, (2) ascertain-
ment of exposure, and (3) exclusion of other diseases that might give similar
symptoms. It should be stressed that recent experience demonstrates that
both the assessment of background exposure and the evaluation of personal
exposure are important.

A full discussion of procedures for the exclusion of other diseases would
 go beyond the scope of this report. It should be stressed, however, that

differential diagnosis at the individual level is important and follows general medical principles. Particular attention should be paid to combinations of symptoms and signs.

It is self-evident that the likelihood of a syndrome being due to carbon disulfide poisoning increases if more of the findings discussed in the previous section are present. Since the changes induced by carbon disulfide involve so many different organ systems, the likelihood of another etiology decreases in proportion to the number of such changes observed. There have been few if any studies concerned with the subclinical stage, systematizing the knowledge that has emerged so far. For this reason it is difficult to find quantitative data. However, a recent study deserves some attention.*

The groups underwent a great number of examinations, but only the following will be considered here: (1) examination of the heart; (2) psychological testing; (3) measurement of the conduction velocities of 8 peripheral nerves (polyneuropathy was considered to exist when two or more nerves showed reduced conduction velocities); and (4) examination of the circulation of the ocular fundus (the criterion for disturbed circulation was delayed peripapillary filling—circumferential, segmental, or both).

The occurrence of isolated and combined signs is shown in Table 1. As many as 59% of the exposed men and 29% of the unexposed men were affected by more than one of the disorders under study. Most combinations occurred more frequently in the exposed group; the combination of 3 abnormalities was 3 times more common in the exposed group and the combination of all 4 abnormalities did not occur at all in the control group. Only 5% of the exposed men, as compared to 31% of the controls, were without any abnormalities. Since disturbance in the choroidal circulation was the most common finding, it seems as if this abnormality represents the earliest effect of carbon disulfide toxicity among those considered here. Tolonen's results show that the etiological role of carbon disulfide can be demonstrated with greater probability the more abnormalities are present at the same time.

Consequently, any monitoring programme should employ as many methods as possible, including, for example, an interview, a clinical examination, an ECG, measurement of the conduction velocity of two or three peripheral nerves, eye examinations, and blood tests, as well as regular measurements of the exposure.

As in all cases of occupational exposure, for the early detection of carbon disulfide intoxication in individual cases, it is essential that all the tests used in the monitoring programme should also be included in the preplacement examination in order to have a base-line for each individual.

TABLE 1. PREVALENCE OF ISOLATED AND COMBINED SIGNS OF CARBON DISULFIDE POISONING IN EXPOSED SUBJECTS AND IN CONTROLS *

<table>
<thead>
<tr>
<th>Signs a</th>
<th>Prevalence (%)</th>
<th>Exposed subjects (n = 97)</th>
<th>Controls (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free of disease</td>
<td></td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>CHD only</td>
<td></td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>EYE only</td>
<td></td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>PN only</td>
<td></td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>BS only</td>
<td></td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>CHD + EYE</td>
<td></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>CHD + PN</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>CHD + BS</td>
<td></td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>EYE + PN</td>
<td></td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>EYE + BS</td>
<td></td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>PN + BS</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CHD + EYE + PN</td>
<td></td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>CHD + PN + BS</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CHD + EYE + PN + BS</td>
<td></td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

Total 100 100


a CHD = coronary heart disease; EYE = delayed papillary circulation; PN = polyneuropathy; BS = behavioural symptoms.

It should be brought to the attention of physicians, especially industrial physicians, that when symptoms, even single, subjective symptoms, related to carbon disulfide intoxication are found, it is important to stop exposure, at least temporarily. The man should be replaced on the job and examined regularly. No further exposure should take place until the symptoms have disappeared.

Studies of the type referred to above are essential to bring order into the interpretation of the various non-specific symptoms and signs of carbon disulfide poisoning. Such studies should be carried out, at least partly, as international cooperative investigations employing standardized techniques.

8.5 Early detection of health impairment due to inorganic lead

Some well-known early reversible effects due to occupational lead exposure in adults are: fall-off in physical fitness, fatigue, sleep disturbances, headache, aching bones, constipation, gastric pain, and decreased appetite. These symptoms are nonspecific, and although they may occur early in the development of lead poisoning they indicate unacceptable overexposure. Before such symptoms occur, early reversible changes in laboratory parameters are manifest. Because lead exerts a typical effect on haem formation,
more specifically on porphyrinogenesis, these symptoms are practically
specific for lead exposure of groups of workers. In cases of chronic exposure,
these parameters provide easily measurable quantitative indicators of
response. In addition, lead in the blood (PbB) and lead in the urine (PbU)
provide quantitative indicators of exposure.

Table 2 shows the approximate relationships between lead exposure and
changes in certain parameters in male workers. It is based upon various
literature surveys. However, it should be clearly understood that the
figures are only approximate; in a group of workers, there will obviously
be differences in exposure and in response between individuals, so that the
figures represent probable averages for groups rather than actual levels in
individuals.

<table>
<thead>
<tr>
<th>Level of occupational exposure</th>
<th>PbB (µg/100 ml)</th>
<th>PbU (µg/litre)</th>
<th>ALAD decrease (%)</th>
<th>PPE (µg/100 ml)</th>
<th>ALAU (mg/litre)</th>
<th>CPU (µg/litre)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-exposed</td>
<td>10-20</td>
<td>&lt; 50</td>
<td>0</td>
<td>&lt; 5</td>
<td>&lt; 150</td>
<td></td>
</tr>
<tr>
<td>Slightly exposed</td>
<td>15-40</td>
<td>&lt; 120</td>
<td>&lt; 70</td>
<td>&lt; 10</td>
<td>&lt; 150</td>
<td></td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>10-70</td>
<td>100-200</td>
<td>60-90</td>
<td>50-200</td>
<td>5-20</td>
<td>100-300</td>
</tr>
<tr>
<td>Excessive exposure</td>
<td>&gt; 70</td>
<td>&gt; 150</td>
<td>&gt; 90</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>&gt; 200</td>
</tr>
</tbody>
</table>

* PbB = lead in blood; PbU = lead in urine; ALAD = aminolevulinic dehydratase activity
  in red blood cells; PPE = protoporphyrin in red blood cells; ALAU = aminolevulinic acid in
  urine; CPU = coproporphyrin in urine.

* Note: limited data on PPE levels are available in the literature; different methods yield
different levels.

On the basis of such data, the Work Conference on Lead, Sub-Committee
on Permissible Limits, of the International Association on Occupational
Health concluded in 1968* that the following levels would indicate acceptable
exposure to inorganic lead in workers: PbB = 70 µg/100 ml; PbU =
130 µg/litre, ALAU = 10 mg/litre; CPU = 300 µg/litre. These levels
correspond to a time-weighted average lead concentration in air of about
150 µg/m³, 40 hours per week. These levels should be regarded as guidelines
for occupational exposure in workers not treated with chelating agents;
they are not applicable to public health exposure. When there is adequate
medical supervision, the above-mentioned levels may be exceeded for short
periods.

Measurement of ALAD is generally too sensitive a method for use in

* ZEILHAUS, R. L. Permissible limits for inorganic lead in industry. In: Proceedings

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occupational health settings; a considerable decrease in ALAD activity may exist long before signs of even moderate exposure appear. If the above-mentioned levels for excessive exposure are not exceeded, a decrease in haemoglobin (Hb) is unlikely to occur in otherwise healthy adult male workers of adequate nutritional status. Increase above these levels, and particularly if accompanied by a decrease in Hb, indicates impending health impairment, ultimately resulting in acute intoxication, or in serious chronic sequelae.

*Basophilic stippling of the erythrocytes* has proved to be a sensitive parameter of the haematological response; however, various proposed techniques produce highly variable results. Counting the number of erythrocytes with basophilic stippling may be particularly worthwhile while for the follow-up of exposed subjects.* a sharp increase may indicate imminent clinical intoxication.

During recent years new findings on the response to inorganic lead in adults with blood levels below 70 µg/100 ml have indicated the desirability of re-evaluating the above-mentioned permissible limits in biological specimens. These findings can be summarized as follows:

1. It is becoming increasingly evident that in adult males an increase in protoporphyrin in erythrocytes (PPE) is an earlier response to disturbed haem synthesis than is an increase of ALA in the urine. Moreover, it has been found that in adult females the increase in PPE occurs distinctly earlier than in adult males, whereas the dose-response curve PbB and PPE is much steeper.*

2. It has already been known for a long time that excessive exposure to lead may entail serious consequences for the peripheral and central nervous systems, such as paralysis and encephalopathy. However, in workers with a PbB level of 70 µg/100 ml, a dose-related decrease in nerve conduction velocity has recently been found. Moreover, there is suggestive preliminary evidence of effects on several psychophysiological and neurophysiological functions.*

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3. Recent preliminary evidence suggests that there is an early decrease in the reduced glutathione content of the erythrocytes and decreases Na$^+$-K$^+$-ATPase activity.¹

4. In workers in the early stages of lead poisoning, some investigators have found an increased rate of chromatid-type aberrations and one-break unstable chromosome changes in peripheral blood; the increase subsided some months after cessation of exposure. In 11 workers who had been exposed for short periods, a follow-up study showed a doubling of the pre-employment rate of abnormal metaphases in the first month of exposure, followed by a further increase in the second month and a stabilization in the next three months; this increase was due both to chromatid changes and to unstable chromosome aberrations. Other researchers have not unequivocally established such chromosome changes.

These four groups of findings suggest the need for caution. However, they should be confirmed in other studies, particularly with regard to the dependence on external and internal exposure levels; moreover, their health significance should be evaluated by a group of experts before recommendations on permissible limits in biological specimens can be made.

The Group proposed a set of procedures to be used in health surveillance in cases of exposure to lead. These procedures are thought to be consistent with the present state of knowledge.

1. To exclude the presence of occupational exposure in a group of workers, evaluation of one parameter may be sufficient. Fairly simple laboratory methods are available: (a) semi-quantitative measurement of coproporphyrin in the urine;² if no individual levels above scale three are present and the group average level is about two, no clearly increased lead absorption exists; (b) measurement of ALA in the urine:³ if in any individual no levels exceed 5 mg/litre, clearly increased lead absorption does not exist; (c) provocation of lead excretion by means of the EDTA test: no impairment of health is likely if the excretion of lead is below 0.8–1.0 mg/24 h.⁴ Both method (a) and method (b) may be undertaken almost completely by technicians in the occupational health field.

2. However, if a lead problem exists, then a more elaborate procedure will have to be applied:

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² Donath, W. F. Arhid za higijenu rada i toksikologiju, 7 : 77 (1956).
(a) **Periodic health examination** in the setting of an occupational health service. The workers should be seen at regular intervals by the physician, who should at least evaluate their subjective health status. In addition, he should measure biological parameters of exposure and/or response: to be preferred are ALA excretion, level of lead in the blood, and haemoglobin. This will give an adequate picture of the intensity of group exposure and will single out subjects with excessive exposure. The frequency of examination depends upon the intensity and stability of exposure and response; no general guide can be given.

(b) **Individuals with excessive exposure and/or response** without manifest intoxication should be studied with more care: evaluation of subjective and objective health parameters, presence of other disease states, and other more or less specific parameters of response to lead, e.g., PPE, haemoglobin, and basophilic granulation. Non-specific parameters may also have to be measured, depending on the needs of the individual, e.g., peripheral nervous function.

3. If a worker presents signs and symptoms of manifest intoxication or of a clinical disease, a full clinical examination may be needed; the complexity and variety of tests depend on the individual need.

4. Concentrations of lead, ALA, and coproporphyrin in the urine are affected by diuresis; a low concentration in a large volume of urine produced may correspond to a high concentration in a small volume of urine. It is therefore necessary either to apply a correction based on specific weight, or to measure at the same time the concentration of creatinine in the urine; the concentrations are then expressed as \( (a) \) corrected concentration = observed concentration \( / (1 - \text{specific weight}) \) or \( (b) \) as amount of lead, ALA, and coproporphyrin per gram of creatinine.

Timed sampling represents another method of correction: the amount of lead, ALA, or coproporphyrin excreted between the last voiding and the preceding one (time interval at least 2–3 hours, preferably longer as in morning urine) is measured: \( \mu g/h \) or \( mg/h \). In this case there is no need for an extra laboratory measurement of creatinine. It has been shown, in the case of exposure to lead, that the intra-individual coefficient of variation for repeated measurements is about the same for timed sampling and for creatinine correction, and considerably less than that for uncorrected concentrations. Timed sampling requires only measurement of the concentration in the last voiding, and of the volume of urine produced, noting down the time of the last two voidings. Measurement of 24-h excretion is not usually feasible in an occupational health setting.
5. Measurement of lead in blood or urine requires a refined laboratory technique; it has been amply shown that even in so-called experienced laboratories the reliability of the measurement may be rather low. Such measurements should be performed in those laboratories that have proved able to produce reliable data. In addition, particularly in the case of lead in urine, great care has to be taken to avoid external contamination (lead-free bottles, no contamination of hands and clothes, etc.). Measurements of ALA and coproporphyrin in the urine and determination of PPE require less elaborate techniques, and are not subject to external contamination.

6. It should be stressed that periodic surveillance of lead workers will not prevent the occurrence of acute intoxication resulting from a very rapid increase in external exposure.

A survey undertaken in the Sudan illustrates the kinds of investigation that can be performed easily in a developing country.

An exposed group of workers was examined to evaluate their response to hazardous exposure by measuring appropriate biochemical variables, including lead in the blood, urinary coproporphyrin, basophilic stippling, and haemoglobin. None of the employees who were clinically examined complained of ill health or showed any evidence of excessive lead absorption. Special examinations were made for the presence of blue lines on the gums, anaemia, or neurological manifestations. A screening test was first done by measurement of urinary coproporphyrin. Those with high levels were selected for measuring lead levels in the blood. A blood film was also examined for basophilic stippling, but all results were negative. The non-exposed group tended to show lower urinary coproporphyrin than the exposed group and workers who were exposed occasionally.

In another factory, 13 workers were examined and 9 of these showed clinical evidence of lead poisoning in the form of fatigue, anaemia, abdominal colic, and other gastrointestinal disturbances. One man showed weakness of the extensors of the right hand. Haemoglobin levels were very low; the highest level in the groups was 92% (13.5 g/100 ml blood) and the lowest level 47% (7.1 g/100 ml blood); 8 showed polychromasia and 2 had basophilic stippling. Most of them showed high coproporphyrin levels in urine. Blood lead was high in most cases; 7 men showed levels above 70 μg/100ml blood, indicating excessive lead absorption. All urinary specimens except one showed dangerous levels of absorption. Urinary lead levels were disproportionately higher than the corresponding blood levels; this could have been due to the very low haemoglobin, which was influenced by other environmental factors. Generally speaking, the clinical picture tended to show a good correlation with the biochemical findings. The group was seen regularly every 15 days for 6 months, during which time the symptoms
disappeared almost completely, haemoglobin levels rose, and urinary coproporphyrin and blood lead levels dropped decisively. From then onwards, the men were seen every 6 months at the specified appointments for their periodic medical examinations. No subsequent rise in the lead biochemical assay was observed.

8.6 Early detection of health impairment due to insecticides

8.6.1 *Organophosphorus insecticides*

The use of this group of insecticides is continually increasing and a number of organophosphorus compounds have been introduced recently as replacements for organochlorine insecticides, the use of which is restricted in many countries. In view of these developments, stricter precautionary measures and regular surveillance of the exposed workers are necessary. The mammalian toxicity of organophosphorus insecticides ranges from relatively low (e.g., malathion) to very high (e.g., mevinphos and parathion). With the exception of a few organophosphorus compounds (no longer in use) that possess a delayed neurotoxic action, organophosphorus compounds do not produce structural damage to the nervous system in mammals. Their toxic action is related to the inhibition of tissue cholinesterases and subsequent accumulation of excessive amounts of acetylcholine at synaptic sites in effector organs. Symptoms of poisoning are mostly of a cholinergic nature.

*Specific phenomena of exposure (absorption)*

Organophosphorus compounds inhibit both erythrocyte cholinesterase (acetylcholinesterase) and plasma cholinesterase (pseudocholinesterase); those used as insecticides are, as a rule, stronger inhibitors of plasma cholinesterase. In contrast to pseudocholinesterase in plasma, the acetylcholinesterase in erythrocytes reflects closely the state of inhibition of acetylcholinesterase in the nervous tissue. Thus, while the inhibition of plasma cholinesterase should be regarded as a very sensitive index of absorption, the inhibition of erythrocyte cholinesterase should be regarded as a specific phenomenon of response, indicating the degree of adverse effect induced in the body.

As normal values for either of the enzymes vary widely, the determination of the pre-exposure values is an important prerequisite for later assessment of the degree of depression. It is the proportionate depression from the normal activity in the individual that is important and not a single numerical value. In this connexion, it should be pointed out that the development of symptoms depends not only on the degree of inhibition but also on the rate
at which it occurs. Studies in people have shown that, in the course of a prolonged exposure to relatively small dosages, a marked reduction, both in plasma and erythrocyte cholinesterase activity, can be observed without any symptoms. This symptomless reduction in cholinesterase activity is made use of in the surveillance of workers occupationally exposed to organophosphorus pesticides.

The following are the hazard levels of cholinesterase depression suggested: acetylcholinesterase activity reduced by 30% of the pre-exposure value requires repeated determinations, after appropriate intervals, and appraisal of the general and individual work situation; acetylcholinesterase activity reduced by 50% of the pre-exposure value requires immediate action, including temporary removal from further exposure and appraisal of the work situation.a

There are a number of methods for the measurement of plasma and erythrocyte cholinesterase. Those most frequently used in the field or laboratory have been reviewed in the sixteenth report of the WHO Expert Committee on Insecticides.b Since the publication of that report there have been no significant developments in this field. However, experience in their use has accumulated, particularly in WHO field trials of newly developed insecticides.c The tintometric method is used most widely as a field method for monitoring exposed workers. By this method, the activities of the two cholinesterases are measured concurrently on a whole-blood sample. WHO is promoting research on the development of a multipurpose field kit that would permit the measurement of erythrocyte and plasma cholinesterase separately, using a spectrophotometric method. This should allow more accurate results to be obtained and, at a later stage, methods for the determination of exposure to other pesticides will be included.

Some exposure tests are available: measurement of the metabolite p-nitrophenol (PNP) in urine following exposure to parathion, methylparathion, chlorothion, and ethylparathion; and of p-nitro-n-cresol following exposure to malathion. The p-nitrophenol test in workers exposed to parathion has proved to be a valid procedure for measuring absorption but not response. The highest excretion occurred at about 6 hours after the last exposure; significant amounts were still detected in urine as long as 10 days after the last exposure; bathing after exposure considerably decreased excretion.d It is not possible to suggest a permissible urinary level, because

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the time course is different from that for cholinesterase. Cases of acute 
poisoning have been reported in subjects with a low excretion of PNP; on 
the other hand, clinical symptoms may be absent notwithstanding high 
PNP excretion. An advance was made recently when a method was deved 
oped for measuring the dimethyl and diethyl phosphates that are metabolites 
of nearly all organophosphorus insecticides. This method is sufficiently 
sensitive to detect metabolites of the most common organophosphorus 
insecticides in the urine of a large proportion of the general population and 
to measure a significant degree of occupational exposure to almost all such 
insecticides.

Changes in various biochemical parameters in the blood have been 
found in epidemiological studies. The pattern has not been a consistent 
one, however, perhaps because of exposure to a combination of various 
pesticides and other toxic agents. A change in protein and amino acid levels 
in serum might be due to disturbed liver function or more probably to an 
adaptive response/enzyme induction; an increase in total serum protein, 
and a change in the albumin/globulin index have been reported; serum 
enzyme activities (aspartato-amino-transferase, aldolase, alkaline phosph 
ase, SGOT, SGPT) were sometimes depressed.

Decreased reabsorption of phosphorus due to impaired renal function 
has been observed in patients more than two weeks after poisoning with 
parathion; this has been attributed to damage to the renal tubules due to 
the metabolite p-nitrophenol.

In workers with long-term exposure, functional effects on the cardio 
vascular system have been found: bradycardia, sinus arrhythmia, raised 
or inverted T wave, disappearance of P wave, hypertension or hypo 
tension.

From this short review of effects, no consistent syndrome emerges; 
the effects are highly non-specific. They are of greater significance, however, 
in studies on groups of subjects if they are found to be more prevalent 
than in non-exposed controls. Probably most or almost all of the effects 
will not appear before inhibition of cholinesterase has taken place. In that 
sense the effects cannot be regarded as early indicators of health impairment. 
In epidemiological studies the various parameters should be studied in order 
to validate the permissible degree of inhibition of cholinesterase. However, 
in recent years, there has been suggestive evidence that at least some of the 
effects mentioned (changes in electrophysiological behaviour of peripheral 
nerves) may occur independently of cholinesterase inhibition.

9 JAGER, K. W., ROBERTS, D. V. & WILSON, A. British journal of industrial medicine, 
8.6.2 Organochlorine insecticides

The most important organochlorine insecticides are DDT, aldrin, dieldrin, endrin, heptachlor, and lindane (hexachlorocyclohexane). Workers are exposed during production, formulation, and application. During production the workers are exposed mainly to one group of closely related compounds, during formulation, and particularly during application, exposure may be to a mixture of various insecticides.

Acute toxicity ranges from high (endrin) to moderate or low (lindane, DDT); because many of the compounds accumulate in the body, long-term exposure may induce pathological responses, possibly with clinically acute signs and symptoms. The compounds are lipophilic and tend to accumulate in fatty tissues (e.g., the nervous system, liver, adipose tissue); responses will also originate in these organs: epileptic convulsions (mainly with aldrin/dieldrin), hepatic disturbances, enzyme induction in the liver. Determination of the concentration in adipose tissues may serve as an index of chronic exposure.

Specific phenomena of exposure (absorption)

For monitoring exposure in workers, measurement of levels in adipose tissue is not an acceptable method. Nor does the determination of organochlorine insecticides or their metabolites in excreta provide a practicable method: excretion of the metabolite DDA correlated only slightly with the length of exposure in workers who sprayed an aerosol containing 3% DDT.

The only practicable method up to now appears to be periodic measurement of organochlorine insecticides in the blood and the following tentative guidelines for DDT and aldrin/dieldrin exposure are proposed: *

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>total DDT</td>
<td>0.2 µg/ml</td>
<td>0.2-0.5 µg/ml</td>
<td>—</td>
</tr>
<tr>
<td>aldrin/dieldrin</td>
<td>0.1 µg/ml</td>
<td>0.1-0.2 µg/ml</td>
<td>&gt; 0.2 µg/ml</td>
</tr>
</tbody>
</table>

Note: Level 1: values below which no harmful effects should be expected.

Level 2: values require action: repeat examination after appropriate interval; guard against exceeding the upper value of this level; appraise general and individual work situation.

Level 3: values require remedial action, including temporary removal from further exposure and appraisal of work situation.

Phenomena of response

Specific phenomena of response are not known. A large body of research is still needed to establish objective, agent-specific, sensitive, and at the same time relevant phenomena of response having a quantitative relationship to exposure.

The non-specific responses observed may be due to many causes, one of which may be the pesticide. Because workers, particularly those employed in formulating plants and in applying pesticides in the field, are usually exposed to a multitude of compounds simultaneously or sequentially, it is still more difficult to evaluate the relationship between exposure to specific agents and specified responses. In all studies, it is important to use adequate controls and to take into consideration seasonal effects, socioeconomic variables, as well as the effects of age, sex, race, and diet, particularly if studies on enzymes are included.

With regard to the assessment of liver function, the following phenomena are the most promising and relevant: serum activity of alkaline phosphatase, aldolase, ornithine carbamoyltransferase; the SGOT/SGPT ratio, and the LDH$_1$/LDH$_4$ ratio. Alterations in serum enzyme activities appear to be more relevant and of more importance if occurring in combination and not as isolated phenomena.

Occupational exposure to some organochlorine insecticides has been shown to induce changes in microsomal activity in the liver. Hepatic enzyme induction accelerates the metabolism of foreign compounds, e.g., drugs (a shortened half-life of phenazone and phenylbutazone has been observed in workers exposed to a mixture of organochlorine insecticides, mainly lindane; an increased metabolism of phenylbutazone has also been reported in DDT-production workers). This may affect the efficiency of drug treatment. The question of whether organochlorine insecticides alter steroid and thyroxine metabolism is of great importance. Studies in workers exposed to DDT or endrin have demonstrated increased breakdown of endogenous corticosteroids; in dieldrin-exposed workers this phenomenon could not be observed. The significance of such changes as an index of response and the relevance for health have still to be established.

Impairment of immunobiological reactivity has been reported in animals; further research is needed on the significance of such effects at occupational exposure levels. Some authors have observed changes in workers' lipoprotein and cholesterol metabolism; further research to assess their significance is needed.

The detection of long-term effects on health should not be based merely upon biochemical studies, but also on a good medical history and clinical examination.
Wherever possible studies of occupationally exposed subjects should include the determination of specific metabolites in urine and the following nonspecific phenomena in order to establish their clinical and epidemiological relevance: blood lipidoid pattern and electrophoretic protein spectrum; biological half-life of appropriate drugs in blood serum and urinary steroid pattern; serum enzyme activities as previously mentioned; neurological examination, including EEG and EMG.

8.7 Early detection of health impairment due to noise

Definition of noise

There are many definitions of noise; for the present purpose, however, it may be regarded as any unwanted sound that may have adverse effects on man. These adverse effects fall in two main categories: extra-auditory effects and auditory effects.

Extra-auditory effects

The extra-auditory effects include reactions of the central nervous and autonomic nervous systems (especially sympathetic reactions), with changes in the peripheral blood flow and blood pressure, metabolic and humoral changes, sleep deprivation, psychological and psychopathological effects, such as increased fatigue and mental health impairment, and other indirect effects, such as annoyance and deterioration of performance. All these are highly integrated effects; some of them can be detected early by methods that are relevant to the biological system concerned and are discussed elsewhere in this report. They are subject to large individual variability and still need further investigation.

Auditory effects

The human ear is subject to certain limitations in regard to the frequencies that it can perceive, as well as to the sound pressures it can detect. A young adult with normal hearing can perceive frequencies from 20 to 20000 Hz, which is called "the audible range of frequencies". The human ear is most sensitive to frequencies in the range 1000–4000 Hz.

The smallest sound pressure that the ear can detect depends on the frequency, but at 1000 Hz this threshold is $2 \times 10^{-9}$ pascals for young adults with normal hearing.

Noise of predominantly high frequency is more damaging to the hearing mechanism than noise of low frequency. Intermittent noise is less damaging than steady state noise, as far as hearing impairment is concerned.
Not only the type, level, and predominant frequencies have an important influence on the effects of noise, but also the duration and distribution of exposure throughout the working day, as well as individual susceptibility.

The auditory effects of noise can be conductive or sensorineural in nature. Only the latter will be considered here since the conductive effects are the result of acute exposures, e.g., rupture of the ear drum by a sudden explosion, and thus have no relation to the principles of early detection. The sensorineural effects include a temporary threshold shift (TTS), which is an immediate consequence of certain exposures to high noise levels and may affect everybody, but is fully reversible in the normal subjects. After repeated excessive exposure, however, full reversal of the threshold shift no longer occurs and a permanent threshold shift (PTS) appears.

Even though it seems clear from numerous studies that there is a striking similarity, at the group level, between the audiogram characteristics of groups that show TTS and those of groups that show PTS after exposure to the same noise, the relationship between TTS and PTS is complex, particularly for individuals. There is a need for further investigation in order to establish a reliable predictive association between the two values. This would provide an extremely valuable contribution to the prevention of noise-induced deafness.

Sensorineural hearing impairment can be detected by audiometric examination. The first sign is a dip in the audiogram at a frequency somewhere between 3000 Hz and 6000 Hz, most usually at about 4000 Hz. The starting point of noise-induced hearing loss is insidious because damage starts in regions of the internal ear that respond to frequencies above the speech range. Thus, this dip in the audiogram is an early sign of hearing impairment and it appears before the individual notices any deficiency. By the time he notices hearing problems, lower frequencies have already become involved and it is then too late to save his hearing for normal communication.

Noise-induced (sensorineural) deafness is irreversible but it is preventable, either through control of excessive noise or by stopping the exposure when the hearing loss is at such an early stage that it does not interfere with normal communication.

The early detection of hearing impairment is fundamental for many purposes:

(a) it gives a warning that hazardous exposure has occurred and that control measures should be taken to prevent noise-induced deafness;

(b) it may serve to indicate that ear protectors are inefficient or inadequately worn, or even, not worn at all;
(c) it is a good means of motivation, because if a worker is informed that a slight dip in his audiogram has been observed, he will take greater care to avoid excessive noise exposure and collaborate more efficiently with the implementation of control measures;

(d) it serves to screen out the more susceptible individuals in the exposed population.

A number of methods have been suggested for disclosing hypersusceptibility to noise but, so far, there is insufficient evidence of their efficacy. Therefore, periodical audiometry remains the most practical method.

An important problem resulting from excessive noise is the interference with communication, which can be determined through environmental measurements and calculations.

Audiometric examinations

Audiometric examinations should be carried out on prospective employees in a noisy working environment on the occasion of the pre-employment (or pre-replacement) examination, and periodically thereafter. The intervals between examinations will depend on the noise exposure, being usually 6–12 months. However, in order to detect hypersusceptible individuals, the first repeat examination should take place after a rather short interval (6–9 weeks).

Audiometric examinations should be performed at least 16 hours after any appreciable exposure to noise. This will ensure that a temporary threshold shift is not regarded as a permanent threshold shift.

Zero hearing loss on the audiometer scale corresponds to the normal threshold of hearing.

Since hearing loss is evaluated through a shift in the threshold of hearing, the ideal situation is to compare the individual with himself before he was exposed to the noise in question. However, it is essential that a standardized reference value (threshold) should be used for all measurements of hearing. A.

Audiometric tests should be performed in a quiet environment, in order to ensure the validity of the test. Noise levels have to be low enough not to interfere with man's hearing threshold.

The following table shows the permissible internal noise level in the audiometric room for the measurement of a 0 dB hearing level at various frequencies:

\[ a \]

\[ b \]

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<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Sound pressure level (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>22</td>
</tr>
<tr>
<td>250</td>
<td>16</td>
</tr>
<tr>
<td>500</td>
<td>18</td>
</tr>
<tr>
<td>1000</td>
<td>26</td>
</tr>
<tr>
<td>2000</td>
<td>36</td>
</tr>
<tr>
<td>3000</td>
<td>39.5</td>
</tr>
<tr>
<td>4000</td>
<td>38.5</td>
</tr>
<tr>
<td>6000</td>
<td>40</td>
</tr>
<tr>
<td>8000</td>
<td>34.5</td>
</tr>
</tbody>
</table>

It should be kept in mind that hearing acuity decreases progressively with age, beginning with the involvement of the highest frequencies. This phenomenon, called presbycusis, should be taken into account when studying audiograms by the introduction of age correction factors, which can be found in the literature.\(^a\)\(^b\)

The various forms of audiology include speech audiology, pure tone air-conduction audiology, and bone-conduction audiology.

**Speech audiology**

Hearing may also be tested using speech sounds, a method that serves to establish any deficiency in hearing speech. Measurement of the "speech reception threshold" consists in determining the sound level (in dB) of spoken words required to enable the individual being tested to hear correctly a stated percentage in a test list.

In recent years studies on the standardization of these procedures have been started.\(^c\)

Some authors have found, by statistical correlation techniques, that the hearing loss in terms of the speech score could be predicted from pure-tone threshold measurements at 500, 1000, and 2000 Hz, which are the most important frequencies for speech.\(^b\) However, further investigation is still required in this field.

Since speech audiology serves to indicate a stage of hearing loss when problems in communication have arisen, it is not of value in the early detection of health impairment.

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Pure tone air conduction audiometry

This is the simple, basic technique, in which a pure tone of controllable intensity and frequency is presented to the ear of the test subjects. Each ear should be tested separately.

The audiometers can present specific discrete (fixed) frequencies, in which case the most usual are 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. There are, also, continuous sweep frequency audiometers, which cover all frequencies within a range, usually from 100 Hz to about 10 000 Hz. This has the advantage that it permits the determination of small and specific dips in the audiogram anywhere in this frequency range, instead of at specific frequencies only.

The audiometric examination may be carried out by placing the individual in a sound field with the known characteristics of frequency and intensity. The use of earphones, however, is much more convenient and much more widespread.

The individual under examination has to respond to the lowest level of sound he can hear in each frequency. Each tone is applied for a period of 1–2 seconds. The usual procedure is to apply them in a systematic order, working from 1000 Hz up to the higher frequencies, then going to the lowest frequency and working upwards to 1000 Hz. Detailed descriptions of audiometric examinations are found in the literature.*

It is important to give clear and consistent instructions. When using the continuous sweep frequency audiometer, the continuous frequency tone must be presented at a level of 15 dB, usually, in the range between 250 Hz to 8000 Hz.

Personnel

Systematic audiometric tests on workers exposed to noise can be performed by well-trained non-medical personnel. Studies have shown no significant difference between the results obtained by fully-trained audiometricians and by people who had carried out only about 30 tests. This indicates that it is not a serious problem to train a person to perform audiometric tests. A reliable, intelligent, and interested person can be in charge of carrying out the audiometric tests, after about 6 hours of training and the performance of some 30–50 tests with surveillance.


b ROBINSON, D. W., loc. cit.
8.8 Conclusions

From the above review, certain points are clear:

1. Many changes are non-specific if observed in an individual worker. However, the specificity may increase when a group of workers is examined and compared with a control group.

2. Many changes are not sensitive if no base-line values are known. The sensitivity can be increased by measuring pre-exposure levels, or by comparison with control groups.

3. The sensitivity and specificity of changes may increase if several parameters are examined at the same time.

4. The specificity of changes will also increase if the hazardous work factor is taken into account, particularly if the exposure is measured quantitatively (degree and duration of exposure), i.e., if health evaluation is combined with environmental monitoring. An epidemiological approach is an integral part of occupational health practice for early detection of health impairment, taking into account the general principles outlined in the report. It is only when health evaluation is combined with environmental monitoring that dose-response relationships can be established.

In preparing guidelines, it is preferable to use an integrative approach more closely related to changes in organ functions. The starting point could be the state of overt ill health, disease, or syndrome that may result from exposure at work, identifying the early stages of these where the manifestations are reversible. One should realize that not all such early stages are reversible, e.g., a change in the audiogram in early occupational hearing loss due to noise, or early radiographic changes in silicosis.

The advantages of such an integrative approach are:

(a) It accounts for both single and multiple causative factors, including those in the working environment and host factors in man.

(b) It is oriented more towards the practical control of health problems through occupational health services, whereas other approaches tend to be somewhat academic.

(c) It lends itself more conveniently to guideline programming in the control of diseases that are highly prevalent in working populations in different countries and makes possible a more realistic priority setting.
9. GENERAL CONCLUSIONS

1. Health evaluation of workers is a necessary procedure for the early detection of health impairment; this may be carried out by general, periodical health examinations, starting with a pre-exposure examination, which provides the baseline for each individual, and by special surveillance procedures aimed at the detection of changes related to specific hazardous exposures; whenever possible, changes that are pre-existent to the early stages of health impairment should be looked for.

2. In preventive medicine in general, the early detection of health impairment at a reversible stage has proved to be a highly effective means. Efforts to increase knowledge in this field should not be limited to occupational exposures. However, the occupational health organization provides an excellent means for developing knowledge in this area. The experience gained is not only of special importance for occupational health practice but also for public health practice and in environmental health programmes.

3. Health evaluation for the early detection of health impairment in occupational exposure to health hazards—due to overload or to underload—is an essential tool for an effective occupational health service. It detects indicators that foreshadow health impairment; it prevents the occurrence of advanced disease and of decreased fitness; it promotes the health of workers; it evaluates the effectiveness of environmental control measures.

4. The information obtained in studies of the toxic effects and health effects of occupational exposure is of potential value for the better understanding of the pathogenesis and etiology of diseases of multiple causation that may not necessarily be occupational in origin, e.g., coronary heart disease.

5. Health evaluation should follow a consistent methodological design, such as that described in this report, in order to increase its effectiveness and permit intercomparison of results and re-evaluation.

6. There is a definite connexion between the criteria of early health impairment and exposure-response relationships upon which maximum permissible limits can be based.

7. The measurement of changes in the levels of agents or metabolites in biological specimens or in physiological parameters provides good indicators of the overall exposure of man to physical, chemical, biological, and psychosocial factors at work and elsewhere. Such measurements are of highly practical value in the evaluation of the magnitude and hazard of exposure. More knowledge and research is required to develop such biological indicators.
8. There is a pressing need for research to elaborate simple and practical diagnostic methods for use in occupational health practice for the early detection of health impairment and exposure.

9. Extensive gaps in knowledge exist with respect to criteria of health impairment, particularly with regard to the combined effects of exposure and underload, psychosocial factors, and host factors (e.g., vulnerable groups).

10. The information now available on the early detection of health impairment has not been applied to a sufficient extent in occupational health programmes, either in industrialized or in developing countries. The lack of training of occupational health personnel may be a factor, as well as a lack of coordination between institutions and between institutions and workers in the field.

10. RECOMMENDATIONS

The Study Group made the following recommendations for action by governments, by WHO, and by occupational health institutions:

A. Action by governments

1. Measures designed to promote the application in occupational medicine of known data on health impairment and exposure, and the creation of health evaluation programmes for the early detection of such health impairment in workers.

2. Encouragement of the establishment and development of occupational health institutes, which should be integrated into the preventive health care organization of the country.

3. Introduction of legislation to improve the efficacy of occupational health programmes for the early detection of health impairment in workers.

B. Action by the World Health Organization

1. Development of a long-term programme aimed at establishing guidelines for the early detection of health impairment resulting from occupational exposure to hazardous work factors, in accordance with the priorities shown in this report (see section 6.4 and Annex 2).

2. Initiation, support, stimulation, and coordination of research programmes aimed at the development of simple and practical diagnostic methods for occupational medical practice.
3. Collation and dissemination of information on means for the early
detection of health impairment, particularly in susceptible groups of
workers.

4. Stimulation and coordination of research programmes, particularly
in regard to: exposure–effect/response relationships; importance of host
factors; health relevance of observed effects; potential effects of combined
exposure to chemical, physical, and psychosocial work factors.

5. Organization of and/or assistance in (a) training programmes in
epidemiological methodology and procedures for the early detection of
health impairment and exposure, and (b) seminars and courses for different
professional groups concerned with occupational health at national,
regional, and international levels.

6. Stimulation of and/or assistance in the development of programmes
for the intercomparison of methods used for the early detection of health
impairment or exposure.

7. Introduction of the concept and practice of early detection of health
impairment into all occupational health programmes assisted by WHO.

8. Improvement in cooperation with other intergovernmental and with
nongovernmental organizations in order to foster an exchange of knowledge,
to coordinate the dissemination of information and the development of
guidelines, and to promote research training.

C. Action by occupational health institutes

1. Research relative to the early detection of health impairment.

2. The development of simple, practical procedures.

3. Promotion of the exchange of information between the occupational
health institutes and practitioners in the field.
Annex 1

PROCEDURES FOR THE HEALTH EVALUATION OF WORKERS IN INDUSTRY AND AGRICULTURE

It is assumed that:

(a) exposure to a specific hazardous work factor has been established;
(b) sufficiently specific biological indices for exposure and effect are available;
(c) permissible limits in biological specimens have been agreed upon;
(d) diagnostic procedures to be applied in the field are available.

Where possible, the following procedures should be adhered to:

1. Biological indices should be measured in all workers before they are exposed. If such measurements are not available, the same indices should be determined at the same time in a control group comparable in respect of age, sex, health status, sociocultural status, and economic level.

2. Measurements should be performed on the same day of the week, at the end of the working day.

3. Diagnostic procedures should be checked regularly for analytical reliability.

4. The frequency of periodic evaluation should depend upon the intensity and stability of the exposure and response, and not on preset rules.

5. The data should be tabulated according to frequency distributions, in order to focus attention on the workers at greatest risk.

6. The frequency distributions should be tabulated in relation to sex, age, duration of employment, disability, and specific conditions of employment (e.g., overtime, shiftwork, department).

7. Since the levels of the indices examined may be subject to seasonal fluctuations, a comparable control group should be studied at the same time.

8. In taking biological specimens, precautions should be taken to avoid contamination from the hands, work room air, or container.

9. For interpretation of the concentrations in urine samples, it may be necessary to have information on the sampling time, specific gravity, or creatinine excretion.
Annex 2

PRIORITIES FOR A LONG-TERM WHO PROGRAMME

The long-term programme proposed by WHO in relation to the early
detection of health impairment in occupational exposure to health hazards,
consists mainly of two types of activity:
A. Reviews and guidelines
B. Research.

A. Reviews and guidelines

These may be based on one of two approaches: they can either start
from syndromes of health effects that are mainly determined by the response
of target organs and biological systems, or they can be based on hazardous
work factors. The reviews should discuss exposure–response relationships,
the effects of combined exposure to hazardous work factors, other work
factors and factors not related to work, and procedures for the detection of
carly health impairment. In addition, they should note gaps in knowledge
requiring further research.

The group agreed on the necessity to prepare the following reviews,
listed in order of priority, within each category:

I. Reviews based upon biological systems and syndromes:

1. Respiratory functions and diseases: many diseases of common
occurrence in working populations result from the inhalation of vegetable
dusts, fibrogenic dusts, irritant gases, vapours, or sensitizing chemicals.
2. Cardiovascular system and diseases.
3. Haematopoietic system and chromosomes and diseases.
4. Central and peripheral nervous system and diseases.
5. Renal system and diseases.

II. Reviews based upon hazardous work factors:

1. Chemical exposures:
   (a) solvents, e.g., chlorinated hydrocarbons, benzene, carbon
disulphide;
(b) metals, e.g., lead, mercury, cadmium, manganese, beryllium, arsenic;
(c) gases, e.g., carbon monoxide;
(d) organic chemicals, e.g., enzymes, insecticides.

2. Physical factors:
   (a) noise;
   (b) vibration;
   (c) non-ionizing radiation;
   (d) atmospheric pressure.

3. Biological factors:
   (a) zoonotic diseases.

4. Other working conditions, including psychosocial factors:
   (a) shiftwork;
   (b) repetitive tasks;
   (c) work responsibility.

B. Research

1. In areas where the above reviews point to gaps in knowledge.

2. On the effects of combined exposure and on host factors.
Annex 3

REVIEW OF EARLY DETECTION OF HEALTH IMPAIRMENT IN OCCUPATIONAL EXPOSURE BASED UPON THE RESPONSE OF ORGANS OR BIOLOGICAL SYSTEMS

A Proposed Outline

1. Anatomy and physiology

   1. Overall review of the anatomy and physiology of the organ or system, with emphasis upon those details that are important in regard to work factors, e.g., mechanisms of absorption and elimination; metabolism; types of response.

2. Adaptive mechanisms

3. Disease syndromes

   If possible, prevalence rates should be given and they should be categorized as follows:
   
   (a) only occupational in origin;
   (b) occupation as one of the causal factors;
   (c) occupation contributes to the occurrence of disease as one of a complex of exogenous factors;
   (d) occupation determines the course of pre-existent disease.

4. Symptomatology

   (a) biochemical and morphological changes;
   (b) changes in physical state and in functional capacities;
   (c) subjective symptoms.

5. Host factors

   (a) age;
   (b) sex;
   (c) pregnancy, lactation;
   (d) incapacities of other systems;
   (e) work-related factors;
   (f) factors unrelated to work.

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6. Hazardous work factors

   Systematic review of hazardous work factors that cause or contribute to a response and of work places where such factors are present. Where possible dose-response relationships or no-response levels for exposure should be given.

7. Procedures for measuring responses

   Two types of procedure are needed: those for detecting manifestations that are pre-existent to early impairment and those for detecting early impairment:

   (a) simple, practical tests for field work;
   (b) tests to be carried out in non-specialized occupational health services or hospitals;
   (c) tests to be carried out in specialized institutions or hospitals.

8. Areas needing further exploration

NOTES

(i) This outline might be adapted according to the specific organ or system reviewed.

(ii) Separate reviews may be needed to deal with separate groups of diseases; several reviews taken together may cover all the responses of a particular organ/system.

(iii) Where possible reference should always be made to more extensive documentation that is readily available.

(iv) Each published review should be of limited size, e.g., a maximum of 70 pages.
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