

SIGNIFICANCE OF LIVER ENZYME DETERMINATIONS IN CHEMICAL WORKERS

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ABSTRACT

A total of 309 men working in the production of fine chemicals and pharmaceutical raw materials underwent medical examinations late in 1975 and again early in 1977. In addition to a thorough physical examination, the assessment of coronary risk factors and a chest X-ray examination, a number of laboratory tests were carried out, among them the liver enzyme determinations of GLDH, GPT, γ -GT and cholinesterase. In the evaluation of the history of each person, particular importance was attributed to the consumption of alcoholic beverages, drug therapy, the incidence of previous liver disease and the exposure to solvents such as methanol, isopropanol, chloroform, acetone, methylene chloride, toluene and others.

In 51 workers (16.5 %) one or several liver function test values were elevated, 13 of these (25.9 %) denied drinking alcoholic beverages, partly because of previous liver and/or gall bladder disease.

Among those with normal liver enzyme activities 58% claimed to be abstinent. Twenty-one per cent took all sorts of drugs regularly for chronic conditions such as hypertension, hypotension, diabetes, ulcers, headaches or rheumatic complaints. The overall incidence of hepatitis and gall bladder disease in the history was only 0.97%. We found cholinesterase to be normal 301 times, 7 times activities were below 3000 U/l (indicative of parenchymal damage) and once an activity of over 9300 U/l (suggestive of fatty liver degeneration) was recorded.

In 17 individuals, there was almost no difference in the liver function values of 1975 and 1977. The remainder showed 16 times a tendency towards lower values and 10 times towards higher values.

Regular measurements of solvent concentration in the air showing extremely low values support the assumption that alcohol consumption represents a much greater risk with regard to hepatotoxicity than solvents, provided the latter are properly handled in "closed systems".

Although organic solvents are used in most branches of present day industry, their use is of particular importance in chemical plants. Thousands and tens of thousands of tons of, for example methanol, are transported yearly into large chemical and pharmaceutical companies, stored, pumped through pipes into various containers, distilled, and re-used for other purposes. There is no doubt that continuous exposure to such organic solvents may cause damage to the health of persons in close contact with these agents.

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Whereas acute intoxication with solvents has become extremely rare, chronic damage is still encountered frequently and must be detected as early as possible.

The determining factor for the intoxication by solvents is the damage to specific organs. Frequently, the metabolites of a solvent are more toxic than the solvent itself, consequently, the metabolism of solvents should not be called "detoxification" in general. Detoxification occurs only whenever a lipid-soluble solvent is changed into a water-soluble compound thus fulfilling the prerequisites for excretion in urine or bile. This alteration shortens the period of a possible toxic effect in the body. Slow solvent metabolism is accompanied by a narcotic stage and the subsequent intoxication is characterized by a typical time lag. Leading symptoms are of a neurotoxic, hepatotoxic and/or cardiotoxic nature. In the case of methanol, for instance, the metabolic half-life is 24 hours. After the narcotic stage, a "free interval" can be observed. Thereafter, intoxication occurs through the effect of formaldehyde and formic acid with the following clinical symptoms: disorientation, convulsions, circulatory collapse and disturbances of vision.

The symptoms of chronic intoxication are quite different (fatigue, headache, dizziness, sleep disturbances, cardiac complaints, reduced alcohol tolerance, nausea and vomiting) and the follow-up of liver studies seems to be one important guide for the detection of chronic damage. Certain solvents cause less parenchymal damage, for instance trichlorethylene or tetrachlorethylene, because their metabolites are not toxic to the liver¹. For the detection of damage, urinary assays must be relied upon. Hepatotoxicity, however, is only part of the damaging effect of solvents, although a very important one, followed by effects on the kidney, the central and peripheral nervous systems, the gastrointestinal tract, the blood and haematopoietic organs.

Since the consumption of alcohol is as important a factor in hepatotoxicity as are solvents², the question remains whether abnormal liver function values in chemical workers reflect damage due to solvents or to alcohol.

SUBJECTS AND METHODS

In our study, we examined 309 chemical workers late in 1975 and early in 1977. In addition to liver enzyme determinations (GLDH, GPT, γ -GT and serum cholinesterase), chest X-ray examination, the assessment of coronary risk factors (including all relevant laboratory tests), urinalysis with Combur-8-Test and a thorough physical examination were carried out. When taking the history, we paid particular attention to the daily consumption of alcoholic beverages, the use of drugs and the incidence of previous liver and/or gall bladder disease plus the exposure time to solvents such as methanol, isopropanol, chloroform, acetone, methylene chloride, toluene and others.

RESULTS AND DISCUSSION

The results of a survey of the consumption of alcohol, the ingestion of drugs and the incidence of hepatitis or gall bladder disease in the history of the

309 chemical workers are presented in Table 1. If one is to believe the statements of all the persons examined, less than half of them consume alcoholic beverages daily. Drugs (mostly tablets for chronic conditions such as hypertension, hypotension, diabetes, gastric or duodenal ulcers, headaches and rheumatic complaints) are taken by more than 20% of the workers in question whereas hepatitis or gall bladder disease occurred in less than 1%.

TABLE 1
Consumption of alcohol, ingestion of medicaments and incidence of hepatitis or gall bladder disease in the history of 309 chemical workers.

| Risk factors | Age (years) | | | | Total | |
|--|-------------|-------|-------|-------------|-------|------|
| | 20-29 | 30-39 | 40-49 | 50 and more | N | % |
| Alcohol | 25 | 41 | 41 | 25 | 132 | 42.7 |
| Medicaments | 12 | 16 | 18 | 19 | 65 | 21.0 |
| Hepatitis and/or gall bladder disease in the history | - | 2 | - | 1 | 3 | 0.97 |

Coronary risk factors were found more often than expected. Table 2 shows the exact incidence.

TABLE 2
Incidence of coronary risk factors in 309 chemical workers.

| Risk factors | Age (years) | | | | Total | |
|-------------------------|-------------|-------|-------|-------------|-------|-------|
| | 20-29 | 30-39 | 40-49 | 50 and more | N | % |
| Cholesterol | 6 | 16 | 19 | 9 | 50 | 16.18 |
| Triglycerides | 3 | 16 | 10 | 8 | 37 | 11.97 |
| Uric acid | 3 | 5 | 9 | 1 | 18 | 5.83 |
| Blood pressure | 1 | 6 | 15 | 11 | 33 | 10.68 |
| Cigarette smoking | 25 | 39 | 28 | 24 | 116 | 37.54 |
| Overweight | 9 | 34 | 43 | 28 | 114 | 36.89 |
| Blood sugar | 2 | 10 | 10 | 11 | 33 | 10.68 |
| Lack of exercise | 28 | 53 | 45 | 24 | 150 | 48.5 |
| 3 and more risk factors | 16 | 34 | 36 | 25 | 110 | 35.6 |

It is noteworthy that more than 1/3 of our group of 309 chemical workers had three and more coronary risk factors. These were determined only in 1975 and were not repeated in 1977. Liver enzyme determinations, in contrast, were carried out twice and revealed abnormal values in 51 cases (16.5%).

Approximately 25% of these persons denied regular consumption of alcoholic beverages. The rest admitted to the consumption of considerable quantities of beer, on the average, 2–3 half-litre bottles per day. In 17 individuals with abnormal liver enzyme values, there was hardly any difference between the determinations in 1975 and 1977. The serum cholinesterase activity was reduced in seven (indicating parenchymal damage) and elevated in one person (suggestive or fatty liver degeneration). In this group, other liver enzyme activities were partly abnormal, partly within the normal range (Table 3).

TABLE 3
Enzyme activities in relation to other parameters.

| Worker | Age (years) | Cholinesterase activity* | GPT (U/l) | | γ-GT (U/l) | | Daily alcohol consumption (number of 1/2l bottles of beer) | Duration of exposure to solvents (years) |
|--------|-------------|--------------------------|-----------|------|------------|------|--|--|
| | | | 1975 | 1977 | 1975 | 1977 | | |
| W.U. | 37 | 2 518 | — | — | 46 | 14 | 1–2 | 8 |
| C.B. | 32 | 2 832 | — | — | 43 | 54 | 1 | 12 |
| E.A. | 38 | 2 884 | — | — | — | — | 1 | 2 |
| E.S. | 52 | 2 852 | 6 | 6 | 18 | 10 | none | 2 |
| H.B.** | 38 | 2 758 | — | — | 26 | 33 | 3 | 13 |
| M.B. | 31 | 2 406 | 5 | 14 | 10 | 11 | none | 5 |
| H.G. | 27 | 2 774 | — | — | 5 | — | none | 9 |
| R.Z. | 29 | 9 716 | 11 | 40 | 242 | — | 4 | 5 |

*Normal values 3 000–9 300 U/l

**Hepatitis at the age of 25

The remainder showed two different tendencies. In 16 persons, the values in 1977 turned out to be lower whereas in 10 persons higher values were found when re-examin was done in 1977. No doubt these changes cannot be termed "improvements" or "deteriorations". Tables 4 and 5 illustrate our results.

In view of the continuous alcohol consumption and the work in a chemical plant with some degree of exposure to solvents it is not possible to say which damage was caused by which noxious agent. However, determinations of solvent concentration in the air helped us a great deal in the interpretation of abnormal liver values. As Table 5 indicates, 20 out of 29 measurements showed no concentration of solvents in the air and the remaining values were well below the permitted levels (200 ppm for methylene chloride, 200 ppm for methanol and 10 ppm for chloroform).

It is obvious from these results that damage by solvents can hardly occur under such circumstances. A series of pictures demonstrating to the workers the way solvents are handled from the moment of their arrival in the company, supports this concept. We believe that the exclusive use of "closed systems"

TABLE 4
Abnormal liver function values in chemical workers.

| GPT(U/l) | | γ-GT(U/l) | | GLDH 1975 | Daily alcohol consumption* | Duration of exposure to solvents (years) |
|----------|--------|-----------|------|--------------|-------------------------------|---|
| 1975 | 1977 | 1975 | 1977 | | | |
| 21 | 18 | 106 | 83 | 6.4 | 4-5 | 15 |
| normal | normal | 45 | 33 | normal | 2 | 9 |
| normal | normal | 53 | 31 | normal | 3 | 9 |
| 29 | 29 | 298 | 199 | normal | 3-4 | 4 |
| normal | normal | 209 | 67 | 12.9 | 5-6 | 9 |
| 17 | 21 | 1049 | 299 | 47.8 | 2-3 | 17 |
| normal | normal | 64 | 39 | normal | 3 | 10 |
| normal | normal | 144 | 53 | normal | - | 15 |
| normal | normal | 220 | 69 | 14.8 | 3 | 2 |
| normal | normal | 43 | 26 | normal | 3 | 20 |
| normal | normal | 113 | 76 | 8.5 | 3-4 | 1 1/2 |
| normal | normal | 75 | 54 | 5.9 | 3-4 | 5 |
| 23 | 10 | 34 | 20 | 14.3 | - | 6 |
| normal | normal | 66 | 36 | 5 | - | 1 1/2 |
| normal | normal | 44 | 35 | 13.6 | 2-3 | 5 |
| normal | normal | 46 | 14 | 6.1 | 2 | 8 |
| normal | 24 | 34 | 42 | 7.7 | 3-4 | 20 |
| normal | normal | 35 | 45 | normal | 3-4 | - |
| normal | 66 | 73 | 92 | normal | 4** | - |
| normal | normal | 43 | 65 | 6.4 | - | 10 |
| normal | normal | 43 | 54 | normal | 1 | - |
| normal | normal | 86 | 104 | normal | - | 25 |
| normal | 25 | 103 | 138 | normal | - | - |
| normal | normal | 179 | 196 | normal | 1 | 2 |
| 11 | 40 | 242 | ? | normal | 4 | 5 |
| normal | normal | 26 | 33 | normal | 3 | 10 |

* 0.5 l bottles of beer

**plus four glasses of hard liquor

helps to minimize toxic damage to organs and leads to the conclusion that damage due to alcoholic beverages probably plays a more important role than that caused by noxious solvents, provided the latter, are handled properly.

Examinations at regular intervals, some of them for the purpose of detecting liver toxicity are mandatory in most branches of modern industry. All persons with abnormal values must be carefully assessed and re-evaluated by specialists in practice or in hospitals.

TABLE 5
Solvent concentrations in the air of a chemical plant.

| June 1978 | Time | Solvent | Solvent concentration (ppm) |
|-----------|-------|--------------------|-----------------------------|
| 2nd | 2.45 | Chloroform | 0 |
| 2nd | 4.00 | " | 0 |
| 5th | 15.00 | " | < 10 |
| 5th | 16.35 | " | 0 |
| 6th | 15.15 | " | 0 |
| 6th | 16.30 | " | 0 |
| 6th | 17.15 | " | 0 |
| 6th | 18.40 | " | 0 |
| 7th | 15.35 | " | 0 |
| 7th | 17.15 | " | 0 |
| 12th | 13.15 | Methylene chloride | 0 |
| 19th | 18.00 | " | 0 |
| 19th | 23.00 | " | 0 |
| 20th | 0.50 | " | 0 |
| 21st | 0.15 | Methanol | 0 |
| 21st | 1.15 | " | 0 |
| 21st | 17.35 | Methylene chloride | 100 |
| 21st | 23.30 | " | < 100 |
| 22nd | 2.45 | " | < 100 |
| 23rd | 0.20 | " | 0 |
| 23rd | 1.45 | " | 0 |
| 26th | 16.40 | " | 100 |
| 26th | 17.45 | " | 0 |
| 26th | 20.00 | " | < 100 |
| 27th | 18.30 | " | 0 |
| 27th | 19.15 | " | 0 |
| 30th | 14.00 | " | ~ 80 |
| 30th | 15.15 | " | 50 |
| 30th | 16.00 | " | < 100 |

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2. *Windemuller, F. J. B. and Ettema, J. H.* Effects of combined exposure to trichloroethylene and alcohol. *Int. Arch. Occup. Environ. Health*, **41** (1978) 77-85.