

Studies on angiopathy due to carbon disulfide

Retinopathy and index of exposure dosages

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SUGIMOTO, K., GOTO, S., KANDA, S., TANIGUCHI, H., NAKAMURA, K. and BABA, T. Studies on angiopathy due to carbon disulfide: Retinopathy and index of exposure dosages. *Scand. j. work environ. & health* 4 (1978) 151—158. The occurrences of retinopathy (microaneurysms/small dot hemorrhages) and the coded resting and postexercise ECG findings suggestive of coronary heart disease (CHD) were studied among 420 Japanese male workers exposed to carbon disulfide and 390 men not exposed to such a solvent. Retinopathy was detected in 24.4 % of the exposed group and in 3.8 % of the nonexposed group by color fundus photography. Among workers of the former group there was a significant correlation between retinopathy prevalences and the index of exposure dosages ($r = 0.925$, $P < 0.01$). However, correlation between the prevalence of retinopathy and duration of exposure was not so high ($r = 0.647$, $0.10 < P < 0.25$). The occurrences of coded resting and postexercise "coronary" ECG findings were not related to the index of exposure dosages. Some risk factors for CHD such as total serum cholesterol, triglycerides, beta-lipoproteins, blood pressure, obesity, and skinfold thickness were simultaneously studied. But these variables did not prove to be important in the development of angiopathy due to carbon disulfide, especially the so-called retinopathia sulfocarbonica.

Key words: blood lipids, carbon disulfide, exercise electrocardiography, exposure dosage index, retinal microaneurysms/small dot hemorrhages, retinopathia sulfocarbonica, skinfold thickness.

In order to clarify questions regarding geographic differences in the development of angiopathy due to carbon disulfide, teams of scientists in Finland, the German Democratic Republic, and Japan have started epidemiologic studies on a

comparative basis. The main objectives of these studies are to observe (a) whether evidence of microangiopathy, especially the so-called retinopathia sulfocarbonica, occurs in European carbon disulfide workers, (b) whether evidence of macroangiopathy, especially coronary heart disease (CHD) attributable to carbon disulfide, is found in Japanese workers, and (c) whether geographic differences in patterns of angiopathy exist, and, if so, to determine why.

Comparisons have already been made of Finnish and Japanese results of electrocardiographic (ECG) (12) and ophthalmological (10) examinations. It was found that (a) the prevalences of coronary ECG findings and reported anginal chest pains

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Table 1. Age distribution of the exposed and nonexposed groups.

Age (years)	Exposed group (N = 420)	Nonexposed group (N = 390)
35-39	188	149
40-44	131	128
45-49	68	68
≥50	33	45
Mean	41.3	42.1
SD	4.7	5.2

did not differ statistically significantly between the carbon disulfide exposed workers in Finland and Japan and (b) Finnish workers showed no retinal changes due to carbon disulfide.

In this paper, the overall results obtained during the first year of study in Japan are presented. We analyzed the retinal findings, ECG abnormalities, obesity, blood pressure, blood lipids (including total serum cholesterol, triglycerides and beta-lipoproteins), and triceps and subscapular skinfolds in relation to the past exposure histories of the workers and put special emphasis on the relationship between retinopathy and the index of exposure dosages.

MATERIAL AND METHODS

The number of workers included in the study were 420 men exposed to carbon disulfide in a rayon filament factory and 390 nonexposed men from a nearby cuprammonium rayon factory. The age distributions of the two groups are shown in table 1. The subjects, whose ages ranged between 35 and 54 years, were randomly selected from their respective population pools. Their medical histories were not taken into consideration in the selection.

The medical examinations included the following:

- personal history concerning occupation, diseases, and smoking habits
- subjective symptoms on carbon disulfide intoxication: headache, feeling of heavy headedness, sleeplessness,

restlessness, forgetfulness, dizziness, nausea or vomiting, impotence, loss of appetite or stomach symptoms, headache during work, feeling of heavy headedness during work, feeling of tiredness or "shibire (numbness)" in the legs, and neuralgia

- standardized angina and infarction questionnaire
- blood pressure
- blood lipids: total serum cholesterol, triglycerides and beta-lipoproteins
- color fundus photography
- electrocardiographic examination before and after exercise on a bicycle ergometer
- anthropometric measurements: body weight, body height, and triceps and subscapular skinfold thicknesses

All the workers fasted for at least 12 h before undergoing the examinations. When the medical histories were recorded, factors of possible importance for the development of vascular lesions, such as hypertension, cardiovascular diseases, nephropathy, athero- or arterosclerosis, and diabetes mellitus, were emphasized.

The workers were interviewed for an accurate occupational history concerning exposure to carbon disulfide, and the data were rechecked against their employment records.

The nonexposed workers were also questioned with respect to subjective symptoms indicative of carbon disulfide intoxication. Our questions were mainly related to the 13 items already listed. An analysis of the symptoms was made in the same manner as that described in our previous paper (2), i.e., two points were given for "feeling of tiredness or 'shibire (numbness)' in the legs" and "neuralgia," and one point for each of the other 11 symptoms. Then the total score of the reported subjective symptoms was calculated for every worker. Thus the total score was weighted towards symptoms of peripheral nerve involvement, which would be important in the diagnosis of chronic carbon disulfide poisoning.

The history of chest pain was recorded with the aid of Rose's questionnaire (7, 13), which allowed for the classification of reported symptoms according to the severity and probability of coronary etiology, i.e., typical, possible, and probable angina

pectoris. The results of reported angina pectoris in the Japanese study have been described elsewhere (12).

The examination included measurements of other variables that many studies suggest to be major risk factors for CHD, namely, smoking habits, blood pressure, blood lipids, obesity and skinfolds. Queries regarding smoking habits were made by questionnaire, the results of which have already been reported (12).

Blood pressure measurements were made according to a standard procedure with a sphygmomanometer and a stethoscope. Blood pressures were measured by the same observer for both groups after the subjects had rested for at least 15 min.

Methods for measuring total serum cholesterol, triglycerides, and beta-lipoproteins in blood drawn from an antecubital vein were as follows: cholesterol, Zak-Henly method (4, 14); triglycerides, acetylacetone method (1); and beta-lipoproteins, immunocrit method (Hyland) (3). All the blood lipids of fresh serum were measured in duplicate. Commercial Versatol controls were also measured daily to eliminate systematic differences within the laboratory.

A well-trained investigator (S. K.) carried out the anthropometric measurements including height, weight and subcutaneous skinfold thicknesses (triceps and subscapular regions). A Harpenden type of caliper was used for the measurement of skinfolds. Additional measurements, such as arm circumference, sitting height, shoulder girdle diameter, pelvic girdle diameter, bone size, etc., were simultaneously performed according to Martin's methods (6). The obesity index (relative body weight) was calculated from the present weight and height, as described in our previous report (12). The body-build and the relative body weight appeared to be the same for both the exposed and the referent group.

Color fundus photography was carried out for 418 exposed and 390 nonexposed subjects. (For two exposed workers it was contraindicated because of glaucoma.) The methods of the examination have been described in detail elsewhere (10). An ophthalmologist (H.T.) read and analyzed the photographs. Microaneurysms and/or small dot hemorrhages, which are the

main findings of so-called retinopathia sulfocarbonica, were recorded.

The ECG response of 406 exposed and 377 nonexposed subjects to single-load submaximal exercise was determined during bicycle ergometry. Excluded were those who did not complete the exercise test and those who were considered medically or physiologically unfit to undergo such stress. The methods of the examination, the reading, and the methods of coding the ECG tracings have been reported earlier (12).

Statistical significance was determined by the *t* test for the quantitative paired comparisons and the chi-square test for the qualitative paired comparisons. Correlation coefficients (*r*) were calculated for the retinopathy prevalence rates and respective exposure category averages; for determining the significance, the *t* statistic was used.

Table 2. Duration of exposure of the exposed group to carbon disulfide.

Duration (years)	Number of subjects (N = 420)
≤4	15
5-9	20
10-14	37
15-19	209
20-24	122
≥25	17
Mean	17.0
SD	5.2

Table 3. Index of exposure dosages for the exposed group.

Index of exposure dosages	Number of subjects (N = 420)
≤49	31
50-99	37
100-149	97
150-199	151
200-249	52
250-299	42
≥300	10
Mean	162.5
SD	69.7

CALCULATION OF THE INDEX OF EXPOSURE DOSAGES

From the available data on carbon disulfide concentration in the polluted departments or at sites at which "exposure" work

is done, the annual changes in exposure levels have been calculated since the commencement of production. Further consideration is also given through time studies of various kinds of jobs in the spinning, xanthation and ripening work-

Table 4. Prevalences (%) of reported diseases in the medical histories of the exposed and nonexposed groups. (Differences between prevalences of both groups did not reach statistical significance according to the chi-square test with Yates' correction for continuity.)

	Diseases				
	Diabetes mellitus	Hyper-tension	Athero-(arterio-) sclerosis ^a	Heart disease ^b	Nephro-pathy ^c
Exposed (N = 420)	0.7	14.3	2.4	1.2	2.6
Nonexposed (N = 390)	0.8	11.5	1.0	0.5	2.3

^a Included arteriosclerosis of the eye, atherosclerosis of the cerebrum and other major arteries except the coronary artery.

^b Included coronary heart disease, valvular diseases, ECG abnormalities and others.

^c Included renal stone disease, pyelonephritis, acute and chronic glomerulonephritis and others.

Table 5. Blood lipids, blood pressure and anthropomorphic data of the subjects in the exposed and nonexposed groups.

Parameter	Exposed (Index of exposure dosages)				Nonexposed (N = 390)
	≤99 (N = 68)	100—199 (N = 248)	≥200 (N = 104)	Total (N = 420)	
Cholesterol (mg/100 ml)					
Mean	174	174	180	175	179
SD	30.5	32.7	37.4	33.7	32.7
Triglycerides (mg/100 ml)					
Mean	119	111	116	114	127
SD	46.8	51.7	48.4	50.3	53.3
β-lipoproteins (mm/60 min)					
Mean	1.9	1.8	1.9	1.9	1.8
SD	0.5	0.5	0.4	0.5	0.5
Systolic blood pressure (mm Hg)					
Mean	122	122	121	122	123
SD	12.3	12.5	13.0	12.6	13.3
Diastolic blood pressure (mm Hg)					
Mean	76	75	75	75	76
SD	8.9	8.9	9.5	9.1	9.5
Obesity index (%)					
Mean	101	101	100	101	102
SD	11.2	11.3	11.0	11.2	11.2
Skinfold					
Triceps (mm)					
Mean	7	7	7	7	6
SD	2.5	2.8	2.1	2.6	2.6
Subscapular (mm)					
Mean	11	12	12	12	11
SD	4.5	4.9	4.8	4.9	5.1

Table 6. Scores assigned the exposed and nonexposed subjects with regard to subjective symptoms indicative of carbon disulfide intoxication.

	Exposed (Index of exposure dosages)			Nonexposed
	≤99 (N = 68)	100-199 (N = 248)	≥200 (N = 104)	
Mean values of scores	3.1	2.9	3.3	2.2
Standard error	0.4	0.2	0.3	0.1

rooms and through changes in job specifications and class of worker's position: the time-weighted annual changes in carbon disulfide concentrations are also computed. Before 1955, the time-weighted carbon disulfide levels in the spinning rooms had varied between 15 and 30 ppm, and after 1955 between 5 and 15 ppm. More details concerning the toxic environment of the plant have been given earlier (12).

The index of exposure dosages (EI) was calculated for every worker from his work history, the time-weighted carbon disulfide concentrations being the criterion. The calculation formula used for the EI was the same as Hernberg's (5). The

distribution of the duration of exposure to carbon disulfide and the EI are shown in tables 2 and 3. The mean value of the exposure duration was 17.0 years, and that of the EI 162.5.

RESULTS

The occurrences of diabetes mellitus, athero- or arteriosclerosis, hypertension, heart diseases, and nephropathy in the medical histories of the exposed group did not differ from those of the nonexposed group (table 4).

There were no differences in the mean values between the workers of exposed

PREVALENCE OF RETINOPATHY

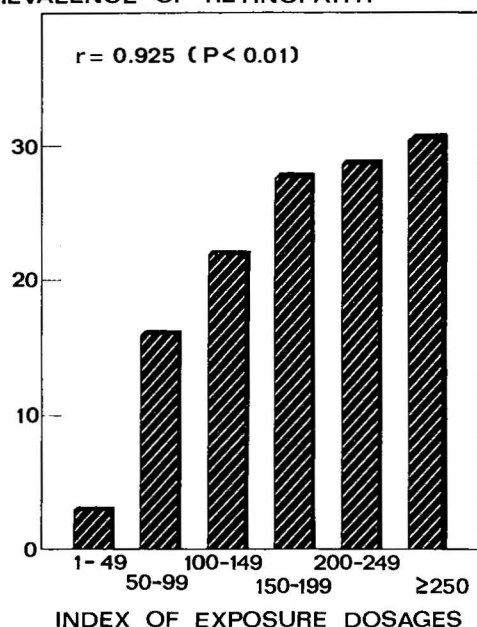


Fig. 1. Index of exposure dosages and prevalence of retinopathy.

PREVALENCE OF RETINOPATHY

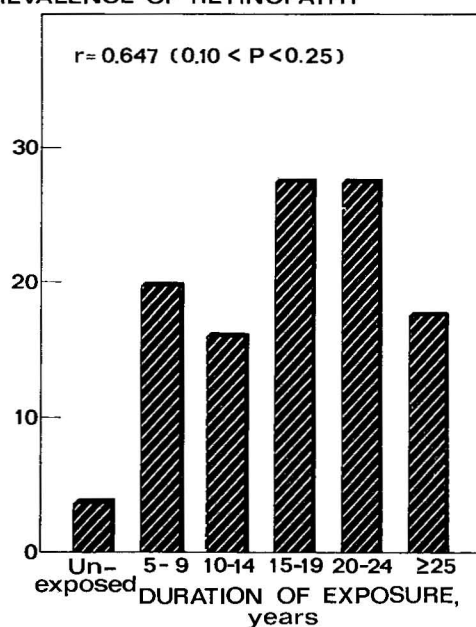


Fig. 2. Duration of exposure to carbon disulfide and prevalence of retinopathy.

Table 7. Prevalences (%) of coded electrocardiographic items indicative of coronary heart disease in the exposed and nonexposed groups in relation to index of exposure (EI) dosages.

Group	EI	"Coronary" ECG codes			Number of subjects
		Resting ECGs			
		1.1—3	4.1—3	5.1—3	
Exposed	≤99	8.8		2.9	68
	100—199	10.9	1.2	6.0	248
	≥200	14.4	1.0	3.8	104
	Total	11.5	1.0	5.0	420
Nonexposed		10.3	0.5	3.6	390
		Exercise ECGs			
		11.1—3	12.1—3	15.1	
Exposed	≤99	1.6	28.1	9.4	64
	100—199	6.3	31.3	9.6	240
	≥200	1.0	21.6	10.8	102
	Total	4.2	28.3	9.9	406
Nonexposed		4.2	22.0	11.9	377

Table 8. Blood lipids, blood pressure and anthropomorphic data of the exposed and the nonexposed with and without retinopathy [R(+) = "with retinopathy," R(−) = "without retinopathy"].

Parameter	Exposed		Nonexposed	
	R(+) (N = 102)	R(−) (N = 316)	R(+) (N = 15)	R(−) (N = 375)
Cholesterol (mg/100 ml)				
Mean	173	176	176	180
SD	33.6	33.7	23.9	33.7
Triglycerides (mg/100 ml)				
Mean	120	111	115	128
SD	49.5	49.7	36.7	54.4
β-lipoproteins (mm/60 min)				
Mean	1.9	1.8	1.8	1.8
SD	0.5	0.5	0.3	0.5
Systolic blood pressure (mm Hg)				
Mean	123	121	132	123
SD	13.7	12.2	14.6	13.8
Diastolic blood pressure (mm Hg)				
Mean	76	75	80	76
SD	9.7	8.8	12.0	9.8
Obesity index (%)				
Mean	102	101	106	102
SD	11.5	11.1	12.9	11.2
Skinfolds				
Triceps (mm)				
Mean	7	7	6	7
SD	2.5	2.6	2.7	2.7
Subscapular (mm)				
Mean	12	12	13	11
SD	4.5	5.0	6.2	4.5

and nonexposed groups in the obesity index, triceps and subscapular skinfold thicknesses, total serum cholesterol, triglycerides, beta-lipoproteins, systolic and

diastolic blood pressures; there were no differences between the mean values of the parameters among the exposed group either (table 5).

The mean values of the scores given every worker were slightly higher for the exposed than for the nonexposed group, but among the exposed workers the scores were not related to the EI (table 6).

The EI and the prevalences of workers with retinopathy showed a highly significant correlation, as shown in fig. 1 ($r = 0.925$, $p < 0.01$). On the other hand, the correlation coefficient between duration of exposure and the prevalences was not so high, as seen in fig. 2 ($r = 0.647$, $0.10 < P < 0.25$).

Table 7 shows the prevalences of the isolated Minnesota codes of the resting and postexercise ECGs accepted as indicative of myocardial ischemia. There was no relationship between each of the prevalences of the isolated Minnesota codes and the EI, nor were there differences between the exposed and nonexposed groups.

In neither the exposed nor the nonexposed group were differences observed in the mean values of the obesity index, skinfolds, blood lipids, and blood pressure of the workers with retinopathy as compared to those without retinopathy (table 8).

DISCUSSION

The noteworthy finding in the study was that the prevalences of retinopathy showed a significantly high correlation with the index of exposure dosages; there was a clear dose-response relationship.

In general, making a quantitative assessment of the dose or even of accumulated exposure is especially difficult for long-term exposure. For the estimation of the dose, the index of exposure dosages was calculated from carbon disulfide concentration data that were available since the commencement of rayon production in the plant and from the work history of every worker at exposure sites. We found that using the EI was better than using the duration of exposure for estimating the actual dosage of past exposure, because the EI reflected changes in exposure levels of individual workers during the course of employment.

In our past epidemiologic studies regarding retinal changes due to carbon

disulfide (8, 9), the duration of exposure, i.e., the length of service in the toxic environment, was used as an estimate of the dose. From the application of the assessment based on duration of exposure a steady increase in retinopathy was evident among workers with less than 20 years of exposure in direct relationships to the length of exposure, but among workers exposed for more than 20 years a decrease in retinopathy prevalence was noted. At the time of our previous studies (8, 9), we had attributed the decrease to drops in exposure levels in terms of intensity and time, due to changes in job specifications and positions in the course of the workers' history. Fortunately in our current study sufficient data concerning the concentration of carbon disulfide were obtained to enable us to base our assessment on the EI rather than on duration of exposure, the latter now being considered less refined than the former.

In a previous paper (8), we reported that exposure to carbon disulfide for more than 5 years had caused retinopathy as an early symptom of chronic carbon disulfide poisoning, at least under existing exposure conditions in Japanese rayon viscose factories. As to the index of exposure dosages, it can be said that an EI of 50 is a significant point in the development of retinopathy due to carbon disulfide, as seen in fig. 1. Roughly speaking, standards 5 ppm of carbon disulfide $\times$ 10 years of exposure, 10 ppm $\times$ 5 years or 20 ppm $\times$ 2.5 years, based on concentration and time, can be considered sufficiently safe for protecting workers from carbon disulfide poisoning.

The pathogenesis for retinopathy caused by carbon disulfide is still unknown. We have been studying the association between disturbance in glucose metabolism (diabetes mellitus) and carbon disulfide exposure for many years. However, decisive evidence has not yet been obtained from past experimental/epidemiologic studies. In the study, blood lipids, blood pressure, obesity, and other variables were checked for a relationship with angiopathy due to carbon disulfide. Previously most of these variables were suggested to be major risk factors for CHD and were related to carbon disulfide exposure too. But our present study did not

reveal any direct association between carbon disulfide exposure and these factors. Thus it can be concluded that long-term exposure to a relatively low level of carbon disulfide does not cause disturbances in lipid metabolism (cholesterol, triglycerides and beta-lipoproteins) or hypertension. In other words, in the development of angiopathy due to carbon disulfide, blood lipids and blood pressure are of no significance, at least in Japanese workers.

The Finnish and Japanese ophthalmologic examinations have clearly shown that the prevalence of retinopathy among the Japanese carbon disulfide workers was exceedingly high, whereas the corresponding prevalences among the nonexposed Japanese and Finns were of the expected order (10). At present we have no evidence to explain why there is such a great difference in the development of retinopathy. We may only suggest that members of the two ethnic groups vary in response to carbon disulfide exposure.

On the other hand, English (11) and Finnish (5) mortality/morbidity studies have made clear the high risk of carbon disulfide exposure to CHD/coronary death. However, in the Japanese carbon disulfide workers a high prevalence of CHD has not yet been observed, i.e., as far as ECG abnormalities suggestive of CHD or reported angina pectoris are concerned (12). In this context, we may have more definitive answers in the future, after the CHD mortality/morbidity studies which are being undertaken in two cohorts formed by our present Japanese groups have been completed. A comparative epidemiologic study by our counterparts in Germany may also shed light on the reasons for such geographic differences in the development of micro- and macroangiopathies due to carbon disulfide.

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