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Vascular effects of carbon disulfide

A review

by MATTI TOLONEN, M.D.¹

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In the words of the great chemist Mendeleev, "Science begins when measure begins; an exact science without measurement is unthinkable" (55). The scientific aspects of medicine place it squarely alongside other sciences in the general search for truth. The humanitarian aspects of medicine include an unflagging devotion to the search for truth in areas where truth is likely to be a statistical resultant based on what is known in law as "best evidence." The "unscientific" nature of medicine becomes evident in the apparently accidental, personal basis that often characterizes discoveries of new occupational, and other, diseases and new concepts of the etiology of common clinical conditions. Rarely do such discoveries occur as a result of systematic efforts and original research, although both of these are essential to the establishment of a doctor's clinical acumen. The inherent variability in biological phenomena calls for a statistical approach and the exercise of extreme care in the acquisition and judgement of data. The time is long past when one man's clinical impression was adequate.

Such thoughts and reasoning are applicable to the history of chronic carbon disulfide (CS₂) poisoning, particularly in regard to the vascular effects of carbon disulfide exposure. However, existing literature in this field is not very conducive to clear thinking. It should emphasize the importance of distinguishing observation from deduction or hypothesis, and, although it is not always easy, a fundamental distinction should be drawn between what is actually found and what is inferred. These warnings appear to have gone virtually unheeded in many investigations on chronic exposure to carbon disulfide and its possible role in the vascular involvement of workers.

It is not surprising that, in the early literature, experts based their hypotheses and conclusions upon scanty or nonexistent evidence drawn from case reports and small clinical series. But even recently published, systematic, cumbersome clinical and epidemiologic investigations with large populations exposed to carbon disulfide have been carried out, compiled, and reported with either a complete lack of knowledge of epidemiologic methods or deliberate neglect of them. Many authors do not even appear to have sufficiently appreciated the difficulty involved in diagnosing a vasculopathy such as coronary heart disease (CHD) or its frequency. An error or an omission in the design of a study has often revealed

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itself after the results have been reported. In this review some examples are given of both well-executed studies and studies in which the authors have drawn unwarranted conclusions as a consequence of biased sampling methods or some other serious methodological flaw.

The present review contains abstracts from past studies that, in my opinion, have directly influenced knowledge of the vascular effects of occupational exposure to carbon disulfide or the development of fruitful concepts. The knowledgeable reader will find that a great deal of the clinically and experimentally oriented work has not been included. This omission is entirely a result of the focus of this review, which is directed towards the vascular effects of exposure to carbon disulfide and is not intended as a compendium of all the work touching upon the toxicology of carbon disulfide.

CHRONIC CARBON DISULFIDE POISONING

Chronic intoxication usually develops during long-term exposure to repetitive, short, high levels of carbon disulfide vapor. The clinical picture of the poisoning takes many forms, and its features vary extremely from one patient to another (70, 71, 77). Normally the disorder begins with general fatigue, headache and dizziness, pain, and numbness in the limbs. These symptoms may gradually become more intense. Behavioral deterioration and toxic polyneuropathy are common findings in overt and latent carbon disulfide (66, 71, 78). A form of presenile arteriosclerosis has been attributed to chronic carbon disulfide intoxication for more than 30 years. This conception has been supported by a number of studies, in which arteriosclerotic changes were produced more readily in animals exposed to carbon disulfide than had been expected by the researchers (36, 77). The lesions also closely simulated the human disease.

BIOLOGICAL MECHANISMS

The biological mechanisms involved in the development of the vasculopathy induced

by carbon disulfide are not yet fully understood. The literature presents at least five different possibilities.

1. Changes in lipid metabolism: Numerous contradictory reports have been made on the cholesterol-raising effect of carbon disulfide exposure. According to many studies (25, 35, 38, 43, 57, 61, 67, 74, 81) serum cholesterol, and particularly its beta fraction, is raised among those suffering from exposure. Some results also seem to indicate an elevated trend for beta lipoproteins (12, 45, 54, 56, 62, 80, 81).

Furthermore, carbon disulfide seems to inhibit or reduce the "clearing factor" (4). This change may then result in the persistent presence of lipoprotein macromolecules in the plasma (4, 6, 62, 78, 80, 81). In a controlled study Ruikka (62) demonstrated that the lipid metabolism of men exposed to carbon disulfide resembled that of men with myocardial infarction.

Changes that occur in lipid metabolism may be related to the intensity of carbon disulfide exposure, as exemplified by the following: Harashima et al. (25) noted higher cholesterol levels in workers exposed chronically to carbon disulfide concentrations of 15 to 65 ppm than in those exposed to 5 to 19 ppm and unexposed workers. More recently the same group (74) reported on a comprehensive survey of carbon disulfide workers in Japan. During 1951 through 1953, when the overall concentrations of carbon disulfide vapor ranged from 40 to 50 ppm, with peak concentrations of 300 ppm or more, an increase was observable in the total serum cholesterol level of exposed workers as compared to that of unexposed workers. In 1965, when the average levels of carbon disulfide vapor in the factory had been reduced to 5 to 15 ppm, with peak concentrations of 100 ppm, the cholesterol levels of exposed workers did not differ from those of the unexposed.

2. Changes in fibrinolytic activity: In animal experiments De Nicola et al. (16, 17) noted increased fibrinolytic activity and, consequently, hypocoagulability. Subsequently other research groups expressed disagreement with these results in studies on exposed and intoxicated carbon disulfide workers (7, 63, 81, 83, 84, 85). According to their reports carbon disulfide seems to decrease fibrinolytic

activity and induce hypercoagulability possibly by inhibiting the activation of plasminogen and inhibiting the plasmin. The differing results of the De Nicola studies may be attributable to the very high concentrations of carbon disulfide.

3. Subclinical hypothyroidism due to interference with the hormonal status of the hypothalamus (8, 46): The authors state that it is not yet known whether carbon disulfide exposure causes primary impairment of thyroid hormone or a consequent deficiency in the thyrotropin stimulating hormone (TSH) or in the TSH-releasing factor or both.

4. Elevation of blood pressure (28, 33, 64, 72): Although the exact nature of this finding is still far from being clarified, one of the many hypotheses advanced can be supported by the studies of Magos et al. (40, 41) that are summarized in no. 5.

5. A toxic effect upon the myocardium: Exposure to carbon disulfide results in small areas of myocardial fibrosis and necrosis in rats (9). Carbon disulfide may also affect the heart and the vessels through interference with the catecholamine metabolism (40, 41). Toxicological studies have indicated that carbon disulfide probably inhibits dopamine- β -hydroxylase, the enzyme which converts dopamine to noradrenaline. In turn changes in the dopamine, tyrosine, and adrenaline levels occur. A high dopamine concentration in the adrenals indicates a derangement in extracerebral catecholamine metabolism, which regulates lipid and glucose metabolism and vasoregulation. These processes are directly or indirectly involved in the development of arteriosclerosis or coronary heart disease. The authors advise caution in the extrapolation of these experimental findings to human responses in industry, but they have presented one biochemical model of the toxicity of carbon disulfide.

Evaluation of the data

The many observations published on the biochemical effects related to carbon disulfide exposure and the development of arteriosclerosis mainly consist of descriptions of comparisons between groups of exposed and unexposed workers and animals, respectively. The contradictory re-

sults obtained by many researchers are apt to create skepticism in regard to the conclusions drawn from the "positive" results. [De Nicola (16, 17) and Visconti et al. (82) can be consulted for details.] The discrepancies are perhaps better explained by the hypothesis that either a different assumption is made about the poison or the results reflect differing levels of exposure, or possibly the different responses of animals and men to carbon disulfide. Nevertheless, the conclusions drawn from the results are subject to criticism. The example of the previously mentioned studies on fibrinolytic activity and consequent hypercoagulability in workers exposed to carbon disulfide should be adequate in this respect. It is inferred that carbon disulfide induces presenile sclerotic changes. Such a conclusion seems totally unjustified since hypercoagulability is best defined as an increased susceptibility of an individual to thromboembolic disease — not as an increased susceptibility to structural changes in the arterial walls.

Valid prospective comparisons, such as that concerning the cholesterol levels between pair-matched exposed and unexposed male workers, have yielded negative results (28, 70). As epidemiologic studies can never confirm a negative relationship, it is necessary to use care in the interpretation of these results if unjustified conclusions are to be avoided.

The interference of carbon disulfide with catecholamine metabolism seems to have been well-established in studies on rats (40, 41), although these results are not, as such, applicable to human responses in the viscose rayon industry.

Recent cross-sectional studies on blood pressure (28, 33, 64, 72) provide weighty evidence for the hypothesis that long-term exposure to carbon disulfide induces rises in both the systolic and diastolic blood pressures. Nonetheless, no knowledge is possessed of the exact biochemical nature of this phenomenon.

To date, our knowledge in regard to the possibility that the biochemical effects of chronic occupational exposure to carbon disulfide lead to arteriosclerotic changes is much too scanty to permit any practical conclusions being drawn. The positive results obtained with small series of both

human and animal studies can be regarded only as supportive evidence for clinical and epidemiologic studies on the relationship between vascular involvements and exposure to carbon disulfide.

PERIPHERAL VESSELS AND CIRCULATION

Using digital plethysmography, rheography and oscillography, Majeron et al. (42) examined the peripheral vasculature of a group of 17 workers exposed to carbon disulfide and 19 subjects with carbon disulfide poisoning. They reported that in the majority of cases the smaller arteries, but also other arteries examined, were sclerotic. No control material was included in the study; it is one example of the many studies (19) on peripheral carbon disulfide vasculopathy which have no control material. To the best of my knowledge the literature contains no controlled, valid study on the peripheral vasculature of circulation in workers exposed to carbon disulfide. Therefore, the concept of peripheral effects of carbon disulfide exposure remains at a stage of individual impression.

CEREBRAL AND GLOMERULAR CIRCULATION

It is generally believed that prolonged exposure to carbon disulfide may lead to both vascular encephalopathy (as a consequence of arteriosclerotic changes) and glomerulosclerosis. This conception has gradually developed from sporadic observations, some examples of which are given in this section. In this context the subject needs to be approached historically to show what has been achieved and what still remains to be done.

As a result of experimental carbon disulfide poisoning, Lewey (36) reported cerebral arteriosclerosis in nine dogs exposed to carbon disulfide; no control group was examined. After 1 year of exposure Vigliani (77) was able to produce hyperlasia and sclerosis in the media and intima of the cerebral arterioles of rats and guinea pigs. Clinical and experimental findings convinced Vigliani that carbon disulfide exposure can lead to atherosclerosis.

As early as 1889 the great neurologist Charcot (10) presented a hemiplegic worker exposed to carbon disulfide. The worker had been diagnosed as having "CS₂ neurosis," a certain form of hysteria. In 1899 Laudenheimer (34) directed his attention to frequent vascular encephalopathy among carbon disulfide workers in Leipzig. However, since the 1940s, when Attinger (5) reported five cases among Swiss viscose rayon workers, cardiovascular and renal involvements (glomerular nephrosclerosis), along with cerebral and general arteriosclerosis, have dominated the clinical features of advanced, chronic carbon disulfide intoxication. All five of the Swiss workers had had marked hypertension and vascular encephalopathy, with serious and even fatal consequences; in addition two exhibited renal failure. Attinger seemed to gain the strong impression that the vascular involvements were the primary lesions in chronic carbon disulfide poisoning. Subsequently Gsell (24), Vigliani (78), and Vigliani and Cazzullo (79) described a particular vascular encephalopathy and renal sclerosis in the autopsy findings of some Italian viscose rayon workers with prolonged exposure to carbon disulfide. Their cases, elderly men who had been exposed to carbon disulfide for more than 15 years, had contracted "vasculopathia arteriosclerotica sulfo-carbonica," the late vascular syndrome of chronic carbon disulfide poisoning.

In 1946 Vigliani (76) reported on the analysis of 100 cases of chronic carbon disulfide poisoning in Italy. During the period from 1946 to 1953, he (77) additionally diagnosed 43 cases of vascular encephalopathy in carbon disulfide workers at four plants in Lombardy. Those patients with chronic encephalopathy exhibited symptoms of pseudobulbar paralysis with mental deterioration, frequent extrapyramidal involvements, and focal signs of cerebral thrombosis. The clinical findings were supported by the electroencephalography and cerebral arteriography of several patients and, in three cases, by autopsy. These results led to the view that the encephalopathy was vascular in origin, and attributable to sclerosis of the small arteries and capillaries of the brain and the spinal medulla.

Human cases of toxic vascular encephalopathy and glomerular nephrosclerosis of the Kimmelstiel-Wilson type ("vas-kulares Spätsyndrom") have been additionally reported by Nunziante Cesaro (53), Uehlinger (75), Vigliani and Pernis (80), Crepet et al. (13, 14), von Rechenberg (61), Vigliani (78), Gobbato et al. (19), Yamagata et al. (87), Sbertoli et al. (65), and experimentally induced carbon disulfide poisoning by Michalová et al. (51). The syndrome was characterized by apoplexia, pyramidal and extrapyramidal symptoms and signs, pseudobulbar paralysis with dementia associated with vascular nephropathy, and hypertension.

The observations made by Vigliani and Pernis (80) led them to the conclusion that the vascular disease appeared in two forms, one affecting the cerebral arteries and the other the renal arteries, the latter of which induces nephropathy and hypertension.

After the clinical examination of 75 viscose rayon workers exposed to high concentrations of carbon disulfide for many years, Martinez and Farina (44) reported that 83 % of the workers had vascular encephalopathy, 22 % disturbed renal function, and 5 % renal hypertension.

As nothing specific had been reported on "vasculopathia sulfocarbonica," in comparison to "natural" general arteriosclerosis and as age introduces a confounding factor in the study of the disease, a joint Yugoslavian and Italian team examined relatively young (30—35 yrs) workers who had been exposed to carbon disulfide for approximately 10 years (47, 48, 49, 68). Their series comprised 104 subjects, of whom 28 were seriously intoxicated by carbon disulfide. After the application of cerebral rheography to the cerebral arteries, the authors reported organic sclerotic changes, mostly in the disabled subjects.

The only epidemiologic approach to the subject is the mortality study of the British Medical Council (69). From 1933 through 1962, 19 deaths from cerebrovascular disease, against the expected 15.6, occurred among rayon process workers.

A recent Finnish neurophysiological study revealed that 21 of the 54 men subjected to exposure had abnormal electro-

encephalograms against 6 of 50 unexposed controls. The result may be interpreted as indicative of toxic lesions in cerebral vessels, but also as indicative of direct toxic action upon the nervous tissue (66).

Evaluation of the data

The large number of similar reports of vascular encephalopathy and nephropathy obtained from several viscose industries may have been regarded by the authors as mutually supportive contributions. This is the enigma that bedevils our understanding and handling of these problems, particularly when the means of objective assessment are impracticable. In a critical analysis of such studies, however, the fact that case studies display the same result does not prove cause and effect; if one looks at all landscapes through a pair of red spectacles, everything looks red. In other words, if the clinician or the pathologist was aware that the patient had been exposed to carbon disulfide, he would be led to a serious consideration of arteriosclerotic or glomerulosclerotic disease, even if the symptoms and (clinical and autopsy) findings were minimal. It follows that arteriosclerotic findings would have been recognized more frequently in workers known to have been exposed to carbon disulfide than would be the case with other subjects. Thus those physicians who accept the belief that carbon disulfide predisposes towards arterio- or nephrosclerosis would have favored the diagnosis of the vascular disease concerned, if the differential diagnosis was difficult, as it frequently is.

A critical reader may perhaps explain the results of most case-report studies by the saying that the suspicion aroused by knowledge of the patient's exposure to carbon disulfide is the sole reason for the manifold increase in the number of diagnosed cases of arteriosclerotic or glomerulosclerotic disease.

To summarize, from a scientific point of view the most serious constraint relates to the lack of reliable and informative control data; the case reports, and the series lacking control, must have included many fortuitous associations. As a consequence, the case reports in themselves prove noth-

ing, but the clinical and experimental data may serve as supportive evidence for a clinical impression and for future epidemiologic investigations.

OCULAR MICROCIRCULATION

The examination of retinal vessels provides a means for the direct investigation of the vascular state *in vivo*. The literature on retinal changes due to carbon disulfide exposure embodies wide experience extending over nearly 30 years. Ever since McDonald's first report in 1938 (50), it has been repeatedly asserted (2, 29, 49) that in animals and humans exposed to carbon disulfide the early signs of intoxication are increased blood pressure in the retinal arteries, general arteriolar narrowing, and caliber irregularities, often termed retinal angiospasm. Accordingly, the authors have suggested direct ophthalmoscopy and the measurement of arterial pressure as aids to the early diagnosis of chronic carbon disulfide poisoning. The absence of a control population, and other methodological flaws in the interpretation of findings, vitiate the arguments presented by the authors, as will be shown in the following discussion.

The ocular syndromes hitherto connected with exposure to carbon disulfide do not provide unequivocal conclusions. In this area the epidemiologic approach has been applied by a Japanese team (20, 21, 22, 29, 30), by a joint Japanese and Yugoslavian group (23), and by a Finnish team (59, 60).

The Japanese researchers have applied objective ophthalmological methods in a study of the effects of carbon disulfide exposure upon the retinal vessels. They used fluorescein angiography (FAG) and color fundus photography. FAG revealed retinal microaneurysms in 109 (55.9 %) of 195 exposed workers (21). The authors did not comment on the undue prevalence of microaneurysms (15.4 %) among the 39 persons in the comparison group. Subsequently, fundus photographs revealed retinopathy in 30.8 % of the 289 exposed workers and in 4.1 % of the 49 members of the comparison group (22).

In the study of the Yugoslavian-Japanese group (23) the comparison group com-

prised a rather small number of subjects — nine. Microaneurysms were found in 30 of the 103 exposed, and in 1 of the 9 unexposed workers.

The Japanese researchers tried to establish the dose-response relationship between carbon disulfide exposure and their findings, but the data on individual exposure have probably been too inaccurate to provide an unequivocal dose-effect curve. Nevertheless, the results indicate a trend toward more retinopathy for those exposed to "high" levels of carbon disulfide than for those exposed to "low" levels (22).

As part of a major epidemiologic study concerned with the health hazards arising from long-term exposure to carbon disulfide in a Finnish viscose rayon factory, Raitta et al. (60) conducted a cross-sectional neuro-ophthalmological study, including ophthalmoscopy and FAG of the ocular fundus. This investigation revealed many things and accordingly deserves closer consideration. The subjects comprised 100 exposed and 97 unexposed men. Signs commonly held as indicative of arteriosclerosis, i.e., the general narrowing and the irregularity of vessel caliber, appeared to be almost equally common in both groups. Narrowing was found in 86 % of the exposed and 85 % of the unexposed; the respective proportions for caliber irregularities were 65 and 81 %. The results thus closely tallied with earlier critical ophthalmological studies (31) in which signs in the fundus oculi, long regarded as diagnostic and prognostic in hypertensive and arteriosclerotic disease, have been shown to be subject to gross inter- and intraobserver errors and bias when assessed by conventional means. Direct ophthalmoscopy proved to be an ineffective method for evaluating the retinal vascular changes induced by carbon disulfide in middle-aged and elderly populations. In FAG the calibers of retinal arteries proved to be permanently wider among exposed than among unexposed subjects, as opposed to the general hypothesis in this respect.

Delayed peripapillary filling in FAG, indicating disturbed choroidal circulation, appeared to be the most interesting finding in this study. The phenomenon was

significantly more common in the exposed group. It was observable in 68 % of the exposed and in 39 % of the unexposed men and did not seem to be related to ageing or raised intraocular pressure, as had earlier been thought (32). The authors attributed this excess "morbidity" to carbon disulfide exposure and assumed that prolonged exposure might induce or promote hemodynamic changes that lead in time to structural alterations at the capillary level.

A subsequent investigation (59) of ocular pulse waves with oculosphygmography (OSG), combined with electrocardiography, supported this assumption. The pattern of ocular pulse wave among workers exposed to carbon disulfide differed markedly from that of unexposed subjects and suggested a decreased flow through the capillaries of the eye.

In view of the existence of a close correlation between the pathological alterations in retinal and cerebral vessels (39) Raitta et al. (50) assumed that the hemodynamic and structural findings observable in ocular microcirculation might reflect similar disturbances in brain circulation.

A disturbance in ocular microcirculation seems to play an important role in the early detection of chronic carbon disulfide poisoning (71). Until recently the occurrence of the several manifestations of subclinical carbon disulfide poisoning within an affected individual had not been studied systematically. In a Finnish study (71) the disturbed ocular microcirculation, indicated by delayed peripapillary filling in FAG, seemed, in fact, to be the first objective finding (of the cardiovascular neurophysiological, neuro-ophthalmological and psychological indicators used in the study) in chronic carbon disulfide poisoning. In this study delayed peripapillary filling always accompanied excess polyneuropathy, excess behavioral deterioration, excess coronary heart disease, and all of their possible combinations. Accordingly a dose-effect relationship logically emerged from this observation. Since delayed peripapillary filling was present in every exposed subject with one or more syndrome induced by carbon disulfide, it was concluded that it was the first omen of chronic, subclinical carbon disulfide poisoning. The solitary

Table 1. Combinations of disturbed ocular microcirculation (EYE), nervous or behavioral deterioration or both (NER), and coronary heart disease (CHD) in male workers exposed to carbon disulfide and in a control group. [Reprinted from TOLONEN, M. *Work-environ.-health* 11 (1974) 159.]

EYE	NER	CHD	Exposed N = 97	Controls N = 96	Difference = Excess morbidity
—	—	+	4	9	-5
—	+	+	4	4	0
—	+	—	17	17	0
+	—	—	19	19	0
+	—	+	4	4	0
+	+	—	30	14	16
+	+	+	17	2	15

findings, and various combinations of the findings, are indicated in table 1.

The results derived by the Finnish team (59, 60) did not in any way tally with those from the Japanese workers in regard to retinal microaneurysms. No evidence whatsoever was found of retinopathy attributable to carbon disulfide exposure in those middle-aged and elderly Finnish viscose rayon workers exposed to the vapor for from 1 to 27 years, with a mean of 15 years. The reason for the different responses between the Japanese and Finnish carbon disulfide workers is unknown. The two research groups have begun a collaborative study with the intention of shedding more light upon the question of microaneurysms.

Evaluation of the data

Nonepidemiologic investigations, employing mainly ophthalmoscopy and ophthalmodynamometry, cannot be considered as valid and reliable in the estimation of the effects of carbon disulfide exposure. There are two fundamental points in favor of this argument: (a) It has been shown that signs regarded as diagnostic in hypertensive and arteriosclerotic disease are subject to gross observer errors when estimated in the conventional way (31). (b) A controlled epidemiologic investigation (60) failed to confirm the earlier allegations based on clinical observation. On the contrary the results supported the criticism

(31) of ophthalmoscopy as a diagnostic examination.

The occurrence of adverse vascular effects as a consequence of carbon disulfide exposure seem to have been established by recent epidemiologic studies. The postulated sequence of events is that carbon disulfide induces disturbed hemodynamics which in turn lead to permanent structural alterations in the capillary bed. The end result is increased scleral rigidity and impaired ocular microcirculation.

The present data enable the conclusion to be drawn that FAG is a necessary examination and that OSG is an important aid in the diagnosis of chronic carbon disulfide poisoning. In regard to retinal microaneurysms, the Japanese and Finnish results seem contradictory. It is to be hoped that a recent, as yet unpublished, joint Japanese-Finnish study will shed new light upon this important subject.

CARDIOVASCULAR EFFECTS

Blood pressure

Since the Pennsylvanian survey in 1938 (35), it has been claimed that chronic exposure to carbon disulfide raises blood pressure. However lack of adequate control groups, and other methodological flaws, make the interpretation of most studies difficult. Nevertheless there exist enough well-executed controlled investigations (28, 33, 64, 72) concerned with relatively large populations to enable the statement that exposure to carbon disulfide raises systolic and diastolic blood pressure.

Angina pectoris

The first comprehensive population study in regard to carbon disulfide was made in the United States. This classic investigation, the "Survey on Carbon Disulfide and Hydrogen Sulfide Hazards in the Viscose Rayon Industry" (2, 35), consisted of a systematic medical examination of 120 viscose rayon workers employed in the state of Pennsylvania. Cardiovascular symptoms were found in one-third of 110 carbon disulfide workers; they complained of

shortness of breath, chest pain, faintness, and poor exercise tolerance.

A standardized questionnaire (86), which allowed the classification of reported chest pain into none, atypical, possible, probable, and typical angina, was first used among carbon disulfide workers by Hernberg et al. (28). In a comparison of 343 exposed and 343 suitably matched unexposed male workers all of the categories of angina were found to be more prevalent among exposed than unexposed men (total angina 17 % and 11 %, respectively). The difference was the most marked for probable angina. At a reexamination 5 years later (72), a similar trend was discerned. On this occasion the difference was the most marked for typical angina (total angina 25 % and 13 %, respectively). The relative and the attributable risks for total angina were 2.2 and 11.6 %, respectively.

"Coronary" electrocardiographic findings

It has been repeatedly reported that the clinical interpretation of electrocardiographic tracings indicates excess coronary heart disease in Japanese (20) and European (11, 38, 73) workers exposed to carbon disulfide. However, the clinical interpretation of the electrocardiograms (ECG) is not a commonly accepted method for population studies (58). Instead a standardized coding procedure is preferred for the avoidance of observer error and variation (18). A recent prospective study (27, 28, 70, 71, 72), in which the ECGs were coded blindly by the application of the Minnesota code, only slightly more frequently revealed "coronary" findings among the exposed subjects than among matched unexposed controls. These slight differences might have arisen by chance.

Nonfatal myocardial infarctions

A 5-year follow-up of the aforementioned cohorts, comprising 343 exposed and 343 unexposed Finnish workers (72), showed that 11 exposed and 4 unexposed men had incurred and survived their first infarction. (The relevant risk factors for CHD had been controlled when this study was initiated.) The relative and attributable risks were 2.8 and 2.2 %, respectively.

Death from myocardial infarction

The British Medical Council's excellent study of deaths resulting from CHD in British viscose rayon workers gave the first strong evidence for a causal relationship between long-term exposure to carbon disulfide and the increased risk of death from CHD (69). The proportional mortality rates, and calculations of observable death rates by type of exposure, showed that in men exposed for 10 years or more, between 1933 and 1962 in a British viscose rayon plant, the risk for death from CHD was 2.5 times that of other workers. Over the 30-year period 42 % of all the deaths of rayon process workers were certified as caused by CHD. The proportion was 24 % for other rayon workers and 17 % for the other local men. The Registrar General's tables showed a national percentage of 14. This proportional mortality was higher from 1943 on, but it declined from 1958 to 1962, and only slightly exceeded that of other local men. The deaths indicated a strong dependence on the intensity of exposure, which had been more pronounced in the 1940s during wartime. Other cardiovascular deaths occurred in eight, against the expected 3.3, process workers aged 35 to 44 years.

In another British factory the death rate from CHD of process operators was 6.1, against the expected 3.2. Twice as many of the spinners died of CHD as had been expected (10 against 4.5). These numbers pointed to an occupational risk in the spinning section (69).

Mowé (52) reported similar results from a viscose plant in Norway. The death rates from the sudden death of exposed workers aged 35 to 54 years was three times that of the unexposed men.

Hernberg et al. (28) observed a proportional mortality from CHD of 52 %, against the expected 31.6 %, among Finnish viscose rayon workers exposed to carbon disulfide for 5 years or more.

All of these mortality studies were retrospective. Thus no control studies could be made of the confounding effects of the risk factors of CHD, such as cigarette smoking, physical activity, dietary habits, and so on.

The aforementioned follow-up study on coronary mortality (72) has contributed to

information on the causality of CHD and the quantity of the risk among workers exposed to carbon disulfide. The cohorts, comprising 343 exposed and 343 unexposed men, have been followed since 1967. During a 5.5-year period 16 exposed men died from CHD against 3 unexposed workers, the odds ratio thus being 5.6. A comparison with national mortality figures showed that the risk of death due to CHD in the exposed cohort was twofold, whereas that of the unexposed group was one-third.

Evaluation of the data

The multiform, and sometimes nonspecific, manifestations of CHD are due to the major difficulties in diagnosing the disease. For example, from the standpoint of electrocardiographic diagnosis considerable intra- and interobserver variation occurs even for experienced cardiologists in the clinical reading of the ECGs (1, 15, 18).

In a population study it is an arduous task to determine the total incidence of CHD. It is self-evident that all possible manifestations of the disease should be taken into account. Obviously this has not been the case in many studies on the subject (11, 20, 37, 38, 73). For example, Lieben et al. (37) have analyzed some data compiled from the medical records of nearly 1,500 viscose rayon workers with 10 years of service or more. This retrospective analysis included a clinical, blind interpretation of an ECG, measurements of blood pressure, total cholesterol, height and weight, and an occupational history. The only difference between the exposed workers and a comparison group (acetate workers) was that of higher blood pressure among carbon disulfide workers. In conclusion the authors stated that no increased risk of cardiovascular involvement existed for those working and exposed to carbon disulfide in the viscose industry concerned. This conclusion is not necessarily true, since the study yielded no evidence on which to base such a conclusion; in reality, it was unwarranted inference. The statement of the authors seems quite inexplicable, since they were aware of the shortcomings in their survey. They stated, "As in all studies of this type, there are shortcomings, and diffi-

culties, and researchers are faced with the alternative of either undertaking and reporting their findings with the shortcomings known to them, or not undertaking the studies." Be that as it may, if the study design includes error and omission, the results must be interpreted accordingly — and with extreme caution.

The data provided by the clinical studies lacking adequate control material are of little, if any, value in the estimation of the causal relationship between carbon disulfide and CHD. Quantification of the risk involved in exposure to carbon disulfide is completely impracticable without epidemiologic methodology. In epidemiologic research on CHD reliance must be placed on simple, carefully standardized methods; however, this procedure lowers the accuracy of the diagnosis on an individual level. For instance, the standard questions on chest pain may elicit positive answers from subjects who are in fact free from the disease. Similarly, some ECG findings that are commonly held to be indicative of CHD are sometimes found in persons without the disease. Accordingly, these milder forms of the manifestations of CHD are more subject to error than are clinical infarction and death.

A trend, indicating that carbon disulfide exposure increases the risk of the serious complications of CHD more than risk of the milder forms of the disease, is observable in the data compiled so far. Nothing is known about the pathological mechanisms of these events, but it has been reasoned (72) that carbon disulfide may accelerate the pathogenesis of CHD or provoke the manifestation of myocardial infarction at a given stage of arteriosclerosis. Carefully controlled autopsy studies are required for the clarification of this problem.

Standardized exercise ECG examinations seem to yield little, if any, useful information from the standpoint of the causality between carbon disulfide and CHD. This may be the case since "coronary" ECGs are relatively nonspecific and insensitive indicators of disease. Nonetheless, an ECG examination should be regarded as an essential part of the periodical health examination of carbon disulfide workers.

SUMMARY AND CONCLUSIONS

Nonepidemiologic studies

Until recently all of the evidence for the hypothesis of a causal relationship between vasculopathy and prolonged exposure to carbon disulfide was gathered from case reports and uncontrolled clinical series. The question the critical reader should ask is whether the conclusions drawn from these studies constitute scientific facts or whether they are mere deductions. If the latter is true, as is clearly the case in many reports, the reader should bear in mind that, although the conclusions appeared valid when they were published, they may later be proven fallacious. From the standpoint of epidemiology all of the case reports and clinical and autopsy series lacked accepted, valid, and reliable means of measurement. Without these ingredients the conclusions remain clinical impressions or highly individual conceptions. Quantification of the risk of vascular lesions — first assessed by the clinical acumen of doctors — proved to be impracticable without epidemiology, even after the initial description of the disease.

In laboratory experiments some scientists have confirmed and extended the observations made in respect to viscose rayon workers. Two are particularly pertinent as a basis for the development of new concepts on the etiology of arteriosclerosis, i.e., those of Lewey (36) and Vigliani (77). Since these animal experiments lacked adequate control, however, it has to be admitted that even these studies did not provide any scientific evidence for support of the hypothesis.

Epidemiologic studies

A thorough search of the literature has revealed that, with the exception of the British Medical Council's study in which cerebrovascular diseases also were considered, epidemiologic studies are related only to disturbed ocular microcirculation and coronary heart disease. Both aspects of these adverse vascular effects are examples of methodological problems involved in seeking for the long-term rela-

tionship between cause and effect and, additionally, dose and response, particularly as the diseases being studied are not uncommon in the general population. In other words changes in blood vessels or their indices are observable even in young persons not exposed to carbon disulfide. Accordingly, the lesions cannot be considered as specific to workers experiencing such exposure.

It should also be borne in mind that a cause and effect relationship between vascular diseases and occupational exposure to carbon disulfide cannot be decided solely on the basis of associations derived from epidemiologic data. These statistical data do not prove causality but simply provide the leads, which need further investigation for the determination of biochemical connections by the compilation of clinical and toxicological data. In the case of exposure to carbon disulfide and vascular disease, enough supportive clinical and experimental evidence has been presented to permit a strong suspicion of a causal association.

Many problems remain to be solved by the epidemiologic approach: (a) the causal relationship between the various forms of vasculopathy and exposure to carbon disulfide needs to be confirmed, (b) the possible causality, i.e., the rates of excess mortality and morbidity, need to be quantified, (c) the role of possible vasculopathy in relation to other manifestations of late responses to long-term carbon disulfide exposure needs to be established, (d) pathogenetic mechanisms need clarification, (e) dose-effect relationships need to be constructed, and (f) a zero-response level of exposure needs to be determined.

The possibility that the available epidemiologic studies will provide solutions to these problems is another matter. First, it is admitted that no direct relevant epidemiologic data exist in regard to vascular encephalopathy possibly induced by carbon disulfide. There are only indirect data suggesting possible toxic lesions in cerebral vessels (60, 66), and a wide gap is present in our knowledge, despite the general concept of vascular encephalopathy as a consequence of carbon disulfide.

Secondly, the problems of establishing causality and quantifying vasculopathy in relation to other manifestations have been

reasonably answered as far as death and morbidity from CHD are concerned (27, 28, 52, 69, 72). The available data enable the statement to be made that exposure to carbon disulfide in the viscose rayon industry introduces a risk of death from CHD which is from 2.5- to 5-fold that of unexposed workers. Furthermore, the only available prospective study (27, 28, 72) has indicated lesser risks for less severe complications of CHD. Accordingly, carbon disulfide exposure seems to accelerate and worsen the development of the disease. Electrocardiographic examinations discriminate poorly, if at all, between exposed and unexposed workers.

For the most part the remaining problems are still unsolved. In my analysis (71) disturbed ocular microcirculation appeared to be the first of all the findings indicative of excess morbidity. The conclusion was thus drawn that it was the first lesion objectively demonstrable even in subclinical carbon disulfide poisoning. Furthermore, the finding seemed essential for diagnosis in my investigation. It should be noted, however, that other methods might have yielded different results. My material must be regarded as too small to permit definite conclusions on the probability of the origin of the various syndromes. Consequently, analyses of other populations would be needed for a clarification of this perplexing but important subject.

In regard to the studies on retinal microaneurysms, the results reported by the Japanese and Finnish research groups seem completely contradictory. It could be argued that these particular studies are only applicable to Japanese viscose rayon workers, but it would be surprising indeed if carbon disulfide did not produce the same alterations in the retinal vessels of workers exposed to approximately the same intensity of carbon disulfide vapor for the same length of time elsewhere in the world. Further, international collaborative studies have been started with the aim of finding the solution to this question.

Epidemiologic studies have contributed very little to the understanding of the pathogenetic mechanisms which lead to vascular alterations. The study of Raitta and Tolonen (59) has to some extent

enhanced the knowledge of changes in the vessels of the ocular fundus. Exposure to carbon disulfide seems to cause diminished blood flow through the ocular vessels, as interpreted from the pattern of the ocular pulse wave. Studies designed to clarify the possible diabetogenic effects of carbon disulfide exposure (20, 21) have not as yet yielded convincing results. The standard glucose tolerance tests used for comparable groups of workers have not revealed any definite disturbances in the glucose metabolism of workers exposed to carbon disulfide (20, 26, 70). It is difficult to assess the justification of the conclusions drawn by Goto's team on the results obtained in their studies on the prednisolone-augmented glucose tolerance test, i.e., that carbon disulfide is a diabetogenic agent leading to the development of retinal microaneurysms. Obviously the point is a debatable one, but it is all-important, as the whole validity of the hypothesis of an association between "retinopatia sulfocarbonica" and the diabetogenic effect of carbon disulfide hinges on it.

Safety considerations

Many attempts have been made to construct a dose-effect relationship between carbon disulfide levels of exposure and the long-term responses measured. So far none of them have been successful, probably because the true concentrations responsible for excess mortality and morbidity have not been available to any research groups. The overall levels of carbon disulfide in the work room atmosphere correlate only roughly and in broad classes — heavy, moderate, and mild exposure — to death from CHD, as shown by Hernberg et al. (27), or to ophthalmological findings as found by Goto et al. (22). From the foregoing, it follows that present knowledge of the dose-response relationship is incomplete and, therefore, that scientifically based standards are difficult to formulate. A large margin of error can affect data based upon such limited information.

The severity of the manifestations of vasculopathy resulting from long-term exposure to carbon disulfide calls for a

serious consideration of the safety margin provided by the current threshold limit value (TLV) of 20 ppm recommended by the American Conference of Governmental Industrial Hygienists (ACGIH). As stated in the *Documentation of the Threshold Limit Values for Substances in Work Room Air* (3), the safety margin of the present TLV may be too narrow to protect the workers from late adverse effects. The TLV of 20 ppm was established to protect the workers from acute psychological and neurological effects due to carbon disulfide vapors. In 1939 the specialists of the Pennsylvanian study (2, 35) proposed a TLV of 10 ppm. In 1972, when the death rates from CHD in the Finnish viscose rayon industry became known, the Finnish TLV was revised to 10 ppm. In view of the large margin of possible error in the dose-response considerations and the serious outcome in chronic carbon disulfide poisoning, i.e., death, it is evident that the current TLV of 20 ppm adopted by ACGIH is an inadequate guide with respect to the late vascular effects of long-term exposure to carbon disulfide.

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