THE LANCET

Vol 338 Saturday 19 October 1991 No 8773

ORIGINAL ARTICLES

Cancer mortality among workers in chemical plant contaminated with dioxin

A MANZ J. BERGER J. H. DWYER D FLESCH-JANYS
S NAGEL H WALTSGOTT

Dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin or TCDD) can arise as a contaminant in the production of herbicides. It causes chloracne in those exposed to it but its human carcinogenicity has been a matter of dispute We report here a mortality follow-up of 1583 workers (1184 men. 399 women) employed in a chemical plant in Germany that produced herbicides. including processes contaminated with TCDD. Production of TCDD was reduced from 1954 after an outbreak of chloracne.

Vital status up to 1989 was determined for 97 1% of workers hired between 1952 and 1984, and 367 deaths (313 men, 54 women) were recorded. A malignant neoplasm was the underlying cause of death in 93 men and 20 women. Standardised mortality ratios (SMR) were calculated with, as references, national mortality statistics for Wesr Germany and deaths in a cohort of male gas workers: for total cancer mortality they were 1 24 .95% confidence interval 1 00–1 52) and 1 39 (1 10–1 75). respectively. among men. Cancer mortality was increased among men with *20* or more years of employment (SMR = 1 87 [Germany] and 1 82 [gas workers]) and among men who began employment before 1955 (SMR = 1 61 and 1 87). The group with suspected highest exposure to TCDD had SMRs of 1·42 and 1·78. Only 7% of cohort women worked in the high exposure locations in the plant compared with 39 6% of men and no increased risk of cancer mortality was observed among women hut breast cancer mortality was raised (SRM = 2 15).

These results. together with a US occupational study and a German investigation of accidental exposure. support the hypothesis that TCDD is a human carcinogen

Lancet 1991, 338: 959-64

Introduction

Although a relation between risk of malignancy at several sites and exposure *to* 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin, TCDD) has been observed in animals,[1-3] the human carcinogenicity of TCDD remains controversial.[4,5] The debate stems primarily from inconsistent findings in case-referent studies relating risk of soft-tissue sarcoma or non-Hodgkin's lymphoma to herbicide exposure. Several investigators have detected a positive association[6-9] but others have not.[10,11] Epidemiological associations between TCDD exposure and other cancers have also been reported.[12-14]

Follow-up of a US cohort of over 5000 TCDD-exposed workers has added substantially to the evidence. Fingerhut et al[14] found an increase in mortality from all cancers (standardised mortality ratio [SMR] = 1·46; 95% confidence interval [CI] 1·21–1·76), and from respiratory cancer and soft-tissue sarcoma in men exposed to TCDD for more than a year and with an opportunity for a minimum latency of 20 years. The finding for all cancers is consistent with a German study of 247 workers exposed to TCDD during a thermochemical accident in 1953.[15] There was a significant increase in total cancer mortality SMR = 2·01 [1·22–3·15]) in the subgroup with chloracne and more than 20 years since exposure.

We describe here a retrospective cancer mortality study of chemical workers employed in an herbicide plant in Hamburg. The plant was heavily contaminated with TCDD from the production of trichlorophenol (TCP) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).

TABLE I—VITAL STATUS BY EXPOSURE GROUPS

Vital status	Exposure group I	II	III	Total
Men				
Unknown	10 (2·1%)	22 (3·5%)	3 (3·8%)	35 (3·0%)
Known alive	349 (74·4%)	442 (69·5%)	46 (58·2%)	836 (70·6%)
Dead	110 (23·5%)	172 (27·0%)	30 (38·0%)	313 (26·4%)
Total	469 (39·6%)	636 (53·7%)	79 (6·7%)	1184 (100·0%)
Women				
Unknown		10 (3·8%)	1 (0·9%)	11 (2·8%)
Known alive	24 (88·9%)	215 (81·1%)	95 (88·8%)	334 (83·7%)
Dead	3 (11·1%)	40 (15·1%)	11 (10·3%)	54 (13·5%)
Total	27 (6·8%)	265 (66·4%)	107 (26·8%)	399 (100·0%)

TABLE II—CAUSES OF DEATH

—	ICD	Men	Women
Observed deaths		313	54
Causes of death known		295 (94·2%)	52 (96·3%)
Malignant neoplasms	140–208	93 (30·2%)	20 (38·2%)
Other natural causes	240–799	172 (55·8%)	28 (53·8%)
Unnatural causes	E800–999	43 (14·0%)	4 (7·7%)
Accident		20 (6·5%)	2 (3·9%)
Suicide		22 (7·1%)	2 (3·9%)
Other		1 (0·4%)	0

Materials and methods

Chemical plant

Public concern over potential hazards from disposal of waste products contaminated with TCDD and other higher chlorinated dioxins led to closure, on June 18, 1984, of a chemical plant in Hamburg-Moorfleet operated by Boehringer-Ingelheim. Production of herbicides began in late 1951. These products included 2,4,5-T, hexachlorocyclohexane (HCH), and lindane. Other products of the plant included dichlorobromophenol and opioids. Synthesis of 2,4,5-T was based upon TCP supplied by a plant in Ingelheim. In response to an outbreak of chloracne in 1954, production of TCP and 2,4,5-T was halted. TCP and 2,4,5-T production were resumed in 1957. Resumption of TCP production was made feasible by a new process that reduced the production of TCDD which, in the meantime, had been identified as a cause of chloracne.

Cohort

The cohort studied consists of all regular employees at the Hamburg-Moorfleet plant who worked under contract with Boehringer-Ingelheim for at least 3 months during the period Jan 1, 1952, to Dec 31, 1984. Temporary or casual workers were not included because of lack of complete information concerning their identity, even though they might have experienced high level acute exposures during clean-up operations. Cohort members were identified from company personnel and union election records, and from employees identified in that way.

Mortality follow-up

Community registries of inhabitants throughout West Germany were used to determine the vital status of cohort members in 1989. Causes of death were derived from medical records. When no medical records were available, death certificates and information from next of kin were used. An experienced nosologist assigned the underlying cause of death according to WHO criteria in the 9th revision of the International Classification of Disease (ICD). All deaths attributed to malignant neoplasms were classified on the basis of medical records.

TCDD exposure

Assessment of exposure to TCDD was based on an analysis of production processes. TCDD concentrations were measured in nonsystematic samples of precursor materials, products, waste, and soil from the grounds of the plant, mainly after the plant had closed in 1984.[16] These indicated TCDD concentrations up to 60 mg/kg in waste from the production of 2,4,5-T. On the basis of this information workers were classified as having had high, medium, or low exposure according to the production departments where they had worked. The numbers were: group 1 (high) 496, group 2 (medium) 901, and group 3 (low) 186.

The validity of these categories was evaluated by analysis of TCDD in adipose tissue from 48 unselected members of the cohort, who volunteered for tests done at the University of Mainz in 1985 (Prof J. Konietzko, personal communication; see also Beck et al[17]). TCDD levels, in ng/kg, averaged 296 (SD 479, median 137) in 37 volunteers in group 1 compared with 83 (SD 73, median 60) for 11 in groups 2 and 3 combined. The median in groups 2 and 3 is higher than the "background" levels of 7–20 ng/kg reported for unexposed persons.[17] TCDD levels in 5 workers in group 1 were below 20, suggesting the possibility of misclassification error; such an error would attenuate any associations between measured exposure and cancer risk.

Chloracne as a marker for TCDD exposure[3,4,18,19] was not used here because information about chloracne in the Boehringer cohort was too incomplete. Chloracne may be fairly specific for TCDD, but it is not very sensitive: Beck et al[17] found that only 10 (28%) of those workers from the Boehringer cohort with adipose levels of TCDD exceeding 20 parts per 10^{12} had a history of chloracne.

Two other variables expected to be related to TCDD exposure are duration of employment at the plant (less than 20, 20 or more years) and year in which employment began (1954 or earlier for it is presumed that those starting work before 1955 would have had higher levels of TCDD exposure).

Comparison groups

Studies with national or regional mortality data as a reference suffer from the "healthy worker" effect—the tendency of cohorts of industrial workers to have a lower risk of early mortality due to cancer and heart disease than the general population. In this study national mortality data were augmented with a second comparison group selected a priori—namely, 3417 male workers at the Hamburg gas supply company, used as controls in a cohort study of furnace workers. This cohort was investigated by some of us,[20] using the same methods to assess vital status and cause of death as with the Boehringer cohort. The follow-up covered the years 1960–85, but was restricted to 1952–85 for comparison with the Boehringer cohort. Amongst the 3120 male workers 1220 deaths were recorded. The follow-up period for the Boehringer cohort was also restricted to 1985. The two cohorts differ in that gas workers had to have worked for at least 10 years to be included while only 3 months of employment were required for the Boehringer cohort. There is no indication of substantial differences in social status between the two cohorts.

Review of medical records

160 medical records from the Boehringer cohort (including 115 cases with a malignant neoplasm at time of death, and 111 medical records from cancer cases of the control group were reviewed by two pathologists (who did not know the cohort status of the cases).

Statistical methods

SMR were calculated by the person-year method.[21] Expected deaths were computed by applying the observed age, calendar year,

TABLE III—SOURCES OF DIAGNOSIS (MALIGNANT NEOPLASMS AND OTHER CAUSES)

Source	Other causes	Malignant neoplasms	Total
Necropsy, histology	82 (25·1%)	69 (61·1%)	131 (36·4%)
Clinical report	85 (34·4%)	32 (28·3%)	117 (32·5%)
Physician report	54 (21·9%)	12 (10·6%)	66 (18·3%)
Other	16 (18·6%)	— (0·0%)	16 (12·8%)
Total	247 (68·6%)	113 (31·4%)	360* (100·0%)

*Deceased with known causes

TABLE IV—STANDARDISED MORTALITY RATIOS (MEN ALL CAUSES) WITH WEST GERMAN NATIONAL DATA AND GAS WORKERS AS REFERENCES

Group	No	West German reference			Gas workers reference*		
		O	E	SMR	O	E	SMR
Total	1140	313	312·8	1·00 (0·89–1·12)	249	186·2	1·34 (1·18–1·51)
Entry ≤ 1954	296	123	131·5	0·94 (0·78–1·12)	102	80·2	1·27 (1·04–1·54)
Entry > 1954	852	190	181·2	1·05 (0·91–1·21)	147	106·0	1·39 (1·17–1·63)
Employment < 20 yr	1030	279	277·0	1·01 (0·89–1·13)	227	164·9	1·38 (1·20–1·57)
Employment ≥ 20 yr	118	34	35·8	0·95 (0·66–1·33)	22	21·3	1·03 (0·65–1·56)

No = number of men. O = observed. E = expected. SMR = standardised mortality ratio with 95% CI.
*In comparison with gas workers Boehringer cohort was restricted to 1985.

sex, and cause specific mortality rates of the gas workers or rates for West Germany to the person-years of the Boehringer cohort. National mortality data were available from the Federal Office of Statistics for most malignant neoplasms of interest, though for some only since 1965. 95% confidence intervals (CI) were calculated assuming the Poisson distribution. The program used for calculations was developed at the Institute of Mathematics and Computer Science, University Hospital Eppendorf, Hamburg.

Results

The Boehringer cohort included 1184 men and 399 women (table I). No company records could be located for 39 men and 14 women identified from union registers or by interview with cohort members. In this group 8 deaths in men and 2 in women were recorded. The date of birth was not available for 1 person.

Vital status was determined for 1537 persons (97·1%) by 1989. 367 deaths were documented (313 men, 54 women; table II). For 7 cases (1·9%) causes of death remained unknown. Table III shows the distribution of sources of diagnosis.

The reviewing pathologists confirmed malignant neoplasm as the underling cause of death in 111 cases (91 men, 20 women). 1 death out of 111 records of the gas worker group was not attributed to cancer. 2 additional cases, confirmed by necropsy, were identified after the review in the Boehringer cohort. 1 additional case of lung cancer in a man who had died in 1958 was reported by his next of kin, but no medical record was available. This case was not included in the statistical analysis. Thus malignant neoplasm was the underlying cause of death in 93 men and 20 women.

Mortality among men

Total mortality equalled that of West Germany (SMR 1·00) but was higher than that in the gas worker cohort (1·34) (table IV). The SMR was slightly greater for those who began employment after 1951 than for those who began before 1955. For the men working up to 20 years SMRs were 1·01 and 1·38 with national and gas-worker data as reference; for the group with more than 20 years, employment SMRs were 0·95 and 1·03, respectively.

Mortality due to malignant neoplasms (table V) was increased with both national (SMR 1·24) and gas-workers (SM 1·39) references. Analysis after division of the Boehringer cohort by year of employment entry revealed an increased SMR for all malignant neoplasms among those who entered in 1954 or earlier (SMRs 1·61 and 1·87) but not for those starting employment later. An increase in risk of cancer death was also found for employment at the plant lasting 20 or more years, SMRs being 1·87 (West Germany) and 1·82 (gas workers). Employment duration and year of entry are highly correlated; nevertheless the cancer mortality risk was more than doubled for those men who both began employment before 1955 and worked at the plant for 20 years or more (table V).

SMRs for exposure group 1 were raised (table VI); increases were also found for group 2 and group 3 but the CIs were large and included unity. The subgroup with time of entry before 1955 high exposure, and employment for 20 or more years had the greatest increase in risk: SMR (West Germany) was 3·5 (1·51, 6·90) for 8 deaths.

Table VII shows SMRs by cancer site. For SMRs (West Germany) there were increases for all sites except colon, but all 95% CIs include unity. In comparison with the gas workers, mortality from lung cancer (SMR 1·67), and haematopoietic cancers (2·65) were significantly increased. On the Kiel classification 6 cases of non-Hodgkin lymphoma were observed (reticulosarcoma 2, lymphosarcoma 1, chronic lymphatic leukaemia 3)—but expected numbers for West Germany were not available.

TABLE V—STANDARDISED MORTALITY RATIOS (MEN, MALIGNANT NEOPLASMS) WITH WEST GERMAN NATIONAL DATA AND GAS WORKERS AS REFERENCES

Duration of employment (yr)	No	West German reference			Gas workers reference*		
		O	E	SMR	O	E	SMR
Total cohort	1148	93	75·2	1·24 (1·00–1·52)	75	53·8	1·39 (1·10–1·75)
Duration of employment							
0–4	653	39	34·9	1·12 (0·80–1·53)	32	23·7	1·35 (0·93–1·91)
5–9	158	14	13·3	1·06 (0·58–1·77)	13	10·2	1·27 (0·68–2·18)
10–19	219	22	17·4	1·27 (0·79–1·92)	17	12·8	1·33 (0·78–2·13)
≥20	118	18	[illegible]	[illegible]	13	[illegible]	[illegible]
Entry ≤ 1954	296	51	31·6	1·61 (1·20–2·12)	33	23·0	1·67 (1·16–2·52)
0–4	157	14	11·6	1·19 (0·65–2·00)	12	7·9	1·53 (0·79–2·67)
5–9	29	5	4·1	1·12 (0·37–2·63)	5	3·7	1·36 (0·44–3·17)
10–19	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≥20	75	17	7·7	2·21 (1·29–3·53)	13	9·6	2·24 (1·19–3·83)
Entry > 1954	852	42	43·6	0·96 (0·69–1·30)	32	30·8	1·04 (0·71–1·47)
0–4	496	25	23·2	1·08 (0·70–1·59)	20	15·8	1·27 (0·77–1·96)
5–9	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
10–19	154	7	[illegible]	0·73 (0·29–1·50)	5	7·1	0·56 (0·15–1·43)
≥20	43	1	1·3	0·52	0	1·7	[illegible]

TABLE VI—STANOARDISED MORTALITY RATIOS (MEN MALIGNANT NEOPLASMS) BY TCDD EXPOSURE GROUP AND WITH *WEST* GERUAN NATIONAL DATA 4ND GAS WORKERS AS REFERENCES

Exposure group	No	West German reference O	E	SMR	Gas worker reference O	E	SMR
Total cohort							
I	454	33	23·7	1·42 (0·96–1·97)	29	20·5	1·76 (1·14–2·55)
II	613	50	45·1	1·11 (0·82–1·47)	59	52·6	1·20 (0·85–1·63)
III	76	9	6·2	1·45 (0·66–2·75)	7	4·8	1·45 (0·58–2·99)
Duration of employment < 20 yr							
I	410	26	20·8	1·25 (0·82–1·83)	22	14·0	1·57 (0·98–2·37)
II	551	41	39·1	1·05 (0·75–1·42)	52	28·2	1·13 (0·73–1·66)
III	69	8	5·6	1·42 (0·61–2·79)	7	4·4	1·60 (0·64–3·29)
Duration of employment ⩾ 20 yr							
I	49	8	3·1	2·54 (1·10–5·00)	7	2·3	3·07 (1·24–6·33)
II	62	9	5·9	1·52 (0·69–2·88)	6	4·4	1·36 (0·50–2·96)
III	7	1	0·6	1·78	0	0·5	
Entry ⩽ 1954							
I	96	18	8·5	2·11 (1·25–3·34)	16	5·7	2·77 (1·59–4·53)
II	173	26	18·8	1·38 (0·90–2·02)	22	13·7	1·61 (1·10–2·44)
III	27	7	4·3	1·64 (0·66–3·39)	5	3·6	1·41 (0·46–3·28)
Entry > 1954							
I	363	16	15·4	1·04 (0·59–1·68)	13	10·6	1·23 (0·65–2·10)
II	440	24	26·2	0·92 (0·59–1·36)	37	46·0	0·80 (0·52–1·44)
III	49	2	1·9	1·03 (0·12–3·71)	2	1·3	1·57 (0·19–5·67)

No death due to soft-tissue sarcoma (ICD 171) was observed

140% of deaths in men were due to unnatural causes (n=43). There were 22 suicides, yielding an SMR of 2·29 (1·38, 3·57) with *West* Germany as the reference and 3·90 (2·42, 5·97) with the gas workers

Mortality among women

The 54 deaths in women yielded an SMR (West Germany) of 0·80 (0·60, 1·05). For malignant neoplasms the SMR was 0·94 (0·58, 1·45) but only the SMR for carcinoma of the breast was raised at 2·15 (0·98, 4·09) for 9 deaths. The 4 deaths due to unnatural causes included 2 suicides. Only 6·9% of women worked in high exposure departments.

Cancer incidence

12 cases of malignant neoplasm in living men were known at the end of the follow-up in 1989. These were prostate, urinary bladder (2), floor of the mouth, larynx, colon, rectum, bronchus, spinocellular carcinoma, melanoma, non-Hodgkin lymphoma, and myeloproliferative syndrome. The men with bronchial carcinoma had myeloproliferative syndrome and a urinary bladder papilloma.

8 malignant neoplasms among living women were breast (5), uterus, pancreas, and colon skin; in 1 case of breast cancer additionally a carcinoma of the skin was diagnosed.

Smoking

Data on smoking were available for a non-representative group of 361 men in the Boehringer cohort. 73% were self-reported smokers. In the gas worker mhon 76% of 2860 men were smokers.

Discussion

Company and union records provided almost complete coverage of the cohort. This, with the mortality follow-up of 97%, makes it unlikely that there is any serious information bias in the Boehringer cohort. In cohort studies there is always the problem which control group is "best". By using gas workers we could better control for the healthy worker effect and occupational exposure to carcinogens. The national mortality data enabled us to identify the magnitude of risk in relation to the population and help comparison of our results with other studies. The use of two standards makes it less likely that the observed effects are due to uncontrolled confounding. The different inclusion criteria for the Boehringer and gas worker groups with respect to length of employment required for entry to the cohort did not seriously bias the results since restricting the comparison to Boehringer workers with duration of employment greater than 10 years did not substantially change the findings.

The national data came from death certificates, whereas in the Boehringer cohort medical records were used. When 190 death certificates in the Boehringer cohort were reviewed, 54

TABLE VII—STANDARDISED MORTALITY RATIOS (MEN BY SITE) WITH WEST GERMAN NATIONAL DATA AND GAS WORKERS AS REFERENCES

Site	ICD	No	West German reference O	E	SMR	Gas workers reference O	E	SMR
Hypopharynx	148	1148	2	1·4	1·42 (0·17–5·14)			
Oesophagus	150	1148	3	1·6	1·86 (0·38–5·44)	2	0·6	3·23 (0·39–11·69)
Stomach	151	1148	12	9·9	1·21 (0·63–2·12)	10	8·9	1·11 (0·54–2·06)
Colon	153–154	1148	8	8·7	0·92 (0·40–1·82)	6	7·9	0·76 (0·28–1·66)
Larynx	161	1148	2	1·0	2·00 (0·24–7·08)			
Lung	162	1148	30	21·3	1·41 (0·95–2·01)	26	15·6	1·67 (1·09–2·44)
Skin	172	1148	1	0·8	1·28	1	1·2	
Prostate	185	1148	7	4·9*	1·42 (0·57–2·93)	5	3·6	1·40 (0·46–3·27)
Kidney	189	1148	3	1·9*	1·56 (0·32–4·56)	4	1·4	2·90 (0·78–7·36)
Haematopoietic system	200–208	1148	7	4·2*	1·67 (0·67–3·44)	9	3·4	2·65 (1·21–5·03)

*References data available only since 1965

the BASF-AG on November 17, 1953. *Am J Ind Med* 1982; 3: 179–89.
14. Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *N Engl J Med* 1991; 199: 212–18.
15. Zober A, Messerer P, Huber P. Thirty-four year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. *Int Arch Occ Environ Health* 1990; 62: 139–57.
16. Kaune A, Fiedler H, Hutzinger O. Dioxine und Furane—Quellen, Eintrag in die Umwelt und Aufnahme durch den Menschen Literaturstudie. Lehrstuhl für Ökologische Chemie und Geochemie der Universität Bayreuth, 1990.
17. Beck H, Eckart K, Mathar W, Wittkowski R. Levels of PCDD's and PCDF's in adipose tissue of occupationally exposed workers. *Chemosphere* 1989; 18: 507–16.
18. Bond GG, McLaren EA, Lipps TE, Cook RR. Update of mortality among chemical workers with potential exposure to higher chlorinated dioxins. *J Occup Med* 1989; 31: 121–23.
19. Zack JA, Gaffey WR. A mortality study of workers employed at the Monsanto Company plant in Nitro, West Virginia. *Environ Sci Res* 1983; 26: 575–91.
20. Manz A, Berger J, Waltsgott H. Zur Frage des Berufskrebses bei Beschäftigten der Gasindustrie—Cohortenstudie. Forschungsbericht Nr. 352 der Bundesanstalt für Arbeitsschutz, Dortmund. Wirtschaftsverlag NW, Bremerhaven, 1983.
21. Breslow NE, Day NE. Statistical methods in cancer research. vol II. The design and analysis of cohort studies. *IARC Sci Publ* 1987; 82: 1–406.
22. Höpker WW, Burkhardt HU. Validitätsuntersuchungen zur amtlichen Todesursachenstatistik. *Verh D Ges Pathol* 1984; 68: 431.
23. Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. *N Engl J Med* 1985; 313: 1263–69.
24. Johnson ES. Association between exposure to phenoxy chlorophenols [illegible] 1990; 14: 213–34.
25. Ott MG, Olson RA, Cook RR, Bond GG. Cohort mortality study of chemical worker with potential exposure to higher chlorinated dioxins. [illegible] 1989; 29: 125–26.
26. Pitot HC, Goldsworthy T, Campbell HA, Poland A. Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from dimethylnitrosamine. *Cancer Res* 1980; 40: 3616–20.
27. Poland A, Palen D, Glover E. Tumour promotion by TCDD in skin of HRS.J hairless mice. *Nature* 1982; 300: 271–73.
28. Lynge E. A follow-up of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br J Cancer* 1985; 52: 259–70.
29. Fitzgerald EF, Weinstein AL, Youngblood LG, Standfast SJ, Melius JM. Health effects three years after potential exposure to the toxic contaminants of an electrical transformer fire. *Arch Envir Health* 1989; 44: 214–21.
30. Boyle CA, Decoufle P, O'Brian TR. Long-term health consequences of military service in Vietnam. *Epidemiol Rev* 1989; 11: 1–27.

Outcome in patients with subarachnoid haemorrhage and negative angiography according *to* pattern of haemorrhage on computed tomography

GABRIEL J. E. RINKEL EELCO F. M. WIJDICKS DJO HASAN
GEORGE E. M. KIENSTRA CEES L. FRANKE LOES M. HAGEMAN
MARINUS VERMEULEN JAN VAN GIJN

15% of patients with spontaneous subarachnoid haemorrhage have normal cerebral angiograms. they fare better than patients with demonstrated aneurysms though rebleeding and cerebral ischaemia can still occur In patients with a normal angiogram and accumulation of blood in the cisterns around the midbrain–"perimesencephalic non-aneurysmal haemorrhage"—outcome is excellent. To ten the hypothesis that rebleeding and disability in angiogram-negative subarachnoid haemorrhage might be limited to those with other patterns of haemonhage on initial computed tomography (CT), complications and long-term outcome were studied in 113 patients with angiogram-negative subarachnoid haemorrhage. admitted between January, 1983. and July. 1990

All patients were investigated with third-generation CT scans within 72 h of the event. and with cerebral angiography The mean follow-up period was 45 (range 6-96) months None of 77 patients with a perimesencephalic pattern of haemonhage on CT died or was left disabled as a result of the haemorrhage (0% [95% confidence interval 0–5%]) Among the other 36 patients, who had a blood distribution on CT indistinguishable from that in proven aneurysmal bleeds. 4 had rebleeds and 9 died or were left disabled as result of the haemorrhage (25% [14–43%])

Thus, two distinct subsets of patients with angiogram-negative subarachnoid haemorrhage should be recognised. Patients with a perimesencephalic pattern of haemonhage have an excellent prognosis. Rebleeding, cerebral ischaemia. and residual disability occur exclusively in patients with aneurysmal patterns of haemonhage on initial CT. Repeated angiography in search of an occult aneurysm is justified only in the patients with aneurysmal patterns.

Lancet 1991; **338**: 964–68.

Introduction

More than half of patients with aneurysmal rupture die or remain severely disabled.[1] Blood in the basal cisterns on computed tomography (CT) strongly suggests aneurysmal rupture,[2] but the cause of the bleed remains uncertain until it is confirmed by cerebral angiography. Despite substantial improvements in imaging acquisition, angiography fails to show an aneurysm in 15% of patients with spontaneous subarachnoid haemorrhage.[3–5] It is widely believed that patients with angiogram-negative subarachnoid haemorrhage have a more favourable prognosis than those with positive angiograms. Nevertheless, they may suffer fatal rebleeds and long-term disability.[3,5,6,8–10]

ADDRESSES University Departments of Neurology, Utrecht (G. J. E. Rinkel, MD, E. F. M. Wijdicks, MD, Prof J. van Gijn, MD), and Rotterdam (D. Hasan, MD, Prof M. Vermeulen, MD); University Department of Neurosurgery, Academic Medical Centre, Amsterdam (L. M. Hageman, MD); and Departments of Neurology, St Elisabeth Hospital, Tilburg (G. E. M. Kienstra, MD), and De Wever Hospital, Heerlen, the Netherlands (C. L. Franke, MD). Correspondence to Dr Gabriel J. E. Rinkel, University Department of Neurology, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.