Papers and Originals

Occupational Toxic Factor in Mortality from Coronary Heart Disease

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Summary: Between 1933 and 1962 42% of 223 deaths of male workers exposed to carbon disulphide in three viscose rayon factories in England and Wales were certified to coronary heart disease—compared with 24% of the deaths in the other workers of the same age, 17% of the deaths in other local men, and 14% in the Registrar General's Tables. Of men with more than 10 years in the rayon industry employed in one of the factories, those exposed to carbon disulphide had death rates from coronary heart disease between 1950 and 1964 two and a half times that of the other workers.

This evidence of an occupational risk of coronary heart disease from long-term exposure to low concentrations of CS_2 was strongest in the 1940s and slight in 1958–62, and it may relate to wartime plant conditions. Current and prospective biochemical and morbidity surveys of exposed workers are now needed. These may also throw light on general issues of atherosclerosis and coronary heart disease.

I. Causes of Death in Three Factories

In the manufacture of viscose rayon some workers are exposed to carbon disulphide (CS_2) and hydrogen sulphide (H_2S). The hazards of exposure to CS_2 were first recognized during the nineteenth century, when it was used as a softening agent in the cold curing of rubber. Many cases of psychosis, encephalopathy, and polyneuritis were reported (Bruce, 1884; Ross, 1886; Oliver, 1902; Legge, 1934). High concentrations of H_2S cause death by respiratory paralysis, but the effects of long-term exposure to low concentrations have not been investigated.

Viscose rayon was first manufactured commercially in 1906. Cellulose is produced from wood pulp and is then mixed with CS_2 in churns to make cellulose xanthate; this is dissolved in caustic soda to form viscose and the men involved may be exposed to CS_2. The viscose solution is then spun into rayon yarn by extruding it through the fine holes of a jet into a bath of sulphuric acid and the yarn is washed and dried. Men who work in the spinning process may be exposed to both CS_2 and H_2S.

From the outset attention was given to the ventilation of workrooms and the enclosure of the processes; later a system of routine monitoring of factory atmospheres for CS_2 and H_2S was developed. In this country poisoning by CS_2 on the scale previously observed in the rubber industry has not occurred in the manufacture of rayon. Since CS_2 poisoning became notifiable in 1924 30 cases have been reported—13 in the rayon industry (Ministry of Labour, 1926–66).

During the past 15 years there have been several reports from other countries of viscose rayon workers developing "atherosclerotic disease" at a relatively early age (Browning, 1965). Vigliani (1954) described cerebrovascular damage with "focal lesions of atherosclerosis" in 43 rayon workers. Thirty-nine of these came from two factories where many cases of polyneuritis due to CS_2 had previously occurred. Others have reported "generalized atherosclerosis," sometimes associated with renal lesions in severely poisoned workers (Attinger, 1948; Nanziante Cesaro, 1953). Alpers and Lewy (1940) observed atherosclerosis in cerebral vessels, as well as polyneuritis, in animals exposed to CS_2. Rabbits exposed to CS_2 200 parts per million for 10 to 20 minutes a day for up to eight months showed changes in the coronary vessels such as thickening of the endothelium, extramural haemorrhages with hyalinization, and sclerosis of the intima (Guarino and Arciello, 1954).

We have not found any report of an occupational risk of coronary heart disease in viscose rayon workers (Ministry of Labour, 1926–66; Vigliani, 1954, Registrar General, 1958; Goldwater, 1960; Warshaw, 1960; Brieger, 1961; Browning, 1965; Brieger and Teisinger, 1967). In view of the clinical observations and animal experiments summarized above we were asked to make a study of mortality from cardiovascular disease in a group of British viscose rayon workers. Since the number at risk was not then available, *death rates* could not be calculated. Instead, the *proportion of deaths* among various rayon workers from cardiovascular disease to be expected on national experience was calculated and compared with the number actually observed among these workers. Thus each group being studied was separately compared with an independent standard.

Methods

The death registers of a municipal borough and the surrounding county in which there were three rayon factories provided the initial data. One factory started manufacturing viscose rayon about 1918 and the other two in 1928 and 1935, respectively.

We extracted for the 30 years 1933 to 1962 the names of all men aged 35 to 64 years at death whose occupation was recorded as rayon worker; exact occupations were obtained from the records of these factories. Of 397 men identified, 223 had been *process workers* employed in the viscose making or spinning processes. The remaining 174 were *non-process workers*—tradesmen, clerks, and general labourers—who in general must have had much less exposure to either CS_2 or H_2S. In terms of physical activity of occupation the process workers on average were probably the more active.

For "controls" we used the 561 deaths of other local men aged 35 to 64 in social classes III, IV, and V (excluding agricultural workers) in the registers of the municipal borough.

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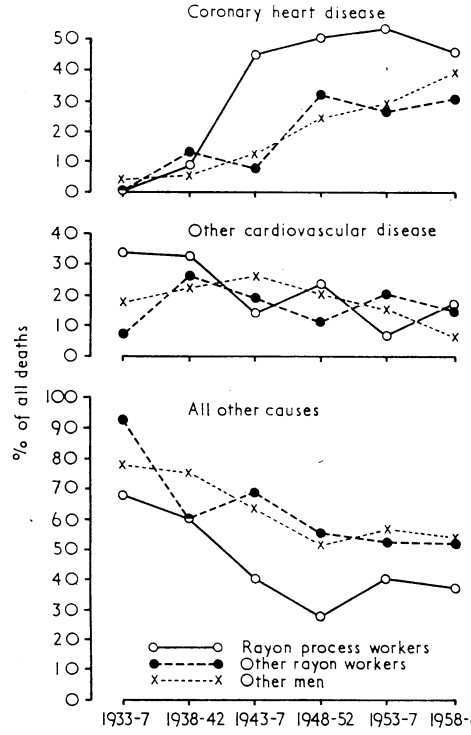
The male deaths for cardiovascular diseases in the area of England and Wales in which the factories are situated are somewhat higher than the national rates, perhaps because the drinking-water is very soft (Crawford, Gardner, and Morris, 1968). We then classified the certified deaths of rayon process workers, other rayon workers, and other local men under three headings: coronary heart disease, other cardiovascular including cerebrovascular disease, and other causes.

Deaths were next allocated to three age groups—35–44, 45–54, and 55–64 years—in each of the six quinquennial periods between 1933 and 1962. The deaths to be expected from coronary heart disease and from other diseases were calculated from the corresponding national mortality data of the Registrar General for each five-year period. For example, in England and Wales there were 116,381 deaths of men aged 45–54 in 1948–52; of these, 18,473 were certified as from coronary heart disease. Over the same period there were 18 deaths in this age range of rayon process workers from all causes in the town and surrounding county that we were studying. The "expected" number of deaths from coronary heart disease at ages 45–54 is $\frac{18,473}{116,381} \times 18$—that is, 2.9. The number actually "observed" was 9.

Results

Over the 30-year period 42% of all the deaths of these rayon process workers were certified to *coronary heart disease*; the proportion was 24% for other rayon workers ($P<0.001$) and 17% for the other local men. Nationally, this fraction was 14%. The proportion among the process workers is higher from 1943, but by 1958–62 is only slightly in excess of that for other local men (see Chart).

Coronary Heart Disease.—Table I gives the observed and expected deaths from coronary heart disease for each quinquennial period; an excess of deaths was found in all three occupational groups. The excess is greatest in the rayon process workers and statistically significant in each age group ($P<0.001$). In the other rayon workers the excess is small and significant only for all ages combined. Coronary deaths among the other local men show similar trends to the rayon non-process workers, but the excess observed is statistically significant at 45–54 years and for all ages together.



Causes of death at ages 35–64 years in rayon workers and other men in social classes III, IV, and V between 1933 and 1962. Deaths have been extracted from the local registers in an area in which three viscose rayon factories are situated; they have been classified under three main causes, using the International Classification of Diseases codes, as follows: coronary heart disease—code 420; other cardiovascular diseases—codes 330–334, 400–416, 421–468.

TABLE I.—*Observed and Expected Deaths from Coronary Heart Disease in Rayon Workers and Other Local Men*

Period	35–44 years		45–54 years		55–64 years		35–64 years	
	Observed	Expected	O.	E.	O.	E.	O.	E.
Rayon Process Workers								
1933–7	0	*0·1*	0	—	0	*0·2*	0	*0·3*
1938–42	0	*0·2*	2	*0·6*	0	*0·4*	2	*1·2*
1943–7	1	*0·2*	7	*0·9*	1	*0·6*	9	*1·7*
1948–52	3	*0·5*	9	*2·9*	8	*2·8*	20	*6·2*
1953–7	2	*0·3*	10	*3·3*	16	*8·0*	28	*11·6*
1958–62	0	*0·2*	8	*4·9*	27	*15·4*	35	*20·5*
1933–62	6	*1·5*	36	*12·6*	52	*27·42*	94	*41·5*
	$P<0·001$		$P<0·001$		$P<0·001$		$P<0·001$	
Other Rayon Workers								
1933–7	0	—	0	*0·1*	0	*0·5*	0	*0·6*
1938–42	0	—	0	*0·2*	2	*0·7*	2	*0·9*
1943–7	1	*0·1*	1	*0·6*	0	*1·7*	2	*2·4*
1948–52	2	*0·2*	4	*1·1*	5	*4·4*	11	*5·7*
1953–7	0	*0·4*	4	*2·4*	8	*6·7*	12	*9·5*
1958–62	0	*0·4*	3	*3·8*	11	*7·6*	14	*11·8*
1933–62	3	*1·1*	12	*8·2*	26	*21·6*	41	*30·9*
							$P<0·05$	
Other Local Men in Social Classes III, IV, and V								
1933–7	0	*0·4*	1	*1·5*	3	*2·7*	4	*4·6*
1938–42	1	*0·2*	4	*2·4*	1	*4·6*	6	*7·3*
1943–7	1	*0·5*	3	*2·1*	7	*6·1*	11	*8·7*
1948–52	0	*0·4*	9	*4·4*	13	*9·5*	22	*14·4*
1953–7	0	*0·7*	11	*5·9*	13	*11·6*	24	*18·2*
1958–62	2	*1·6*	9	*5·2*	19	*13·5*	30	*20·2*
1933–62	4	*3·9*	37	*21·5*	56	*48·0*	97	*73·4*
			$P<0·001$				$P<0·01$	

Notes: (1) "Expected" deaths derived from the proportion *coronary heart disease deaths : all deaths* in England and Wales (for details see text). (2) Each excess of deaths was tested for statistical significance by chi square, using the difference between the observed and expected deaths from other causes as well as coronary heart disease. (3) The expected deaths from coronary heart disease may be calculated by another method (Doll, 1958). Deaths from other causes are multiplied by the ratio of deaths from coronary heart disease to deaths from other causes in England and Wales. This gives a lower "expected" figure. (4) In this and subsequent Tables P values are given only when less than 0·05.

Other Cardiovascular Disease.—Rayon process workers aged 35–44 had eight deaths against 3.3 expected ($P<0.02$); this was the only statistically significant excess observed in any of these groups. The rayon process workers had 19 deaths from *cerebrovascular disease* against 15.6 expected, but this excess might well have occurred by chance.

Older Rayon Workers.—Deaths of rayon workers at ages 65–74 were also extracted; there was no excess of certified deaths from coronary or cerebrovascular disease in either the process or the non-process workers.

Further Test.—In a small viscose rayon factory in another county the records of the personnel department showed that 38 employees had died between 1951 and 1960, and all but two of the death certificates were traced. Fourteen had been process workers, and nine of them aged 31 to 58 died of coronary heart disease. Four of the 22 deaths in non-process workers were certified as coronary heart disease, at ages 56 to 77. The difference between these proportions is significant ($P<0.01$).

Comment

This preliminary reconnaissance of cardiovascular mortality is defective in several respects. "Process" workers had to be treated as a homogeneous group and the relative risk in the viscose making and spinning processes was not assessed. Moreover, we did not examine risk in relation to length of exposure.

"Other males" from the same area were not altogether suitable as controls, since they included men who had previously been process workers in the rayon factories. The exact number of these is not known, because it was impracticable to link all death register entries with factory employment records. However, superficial examination of records back to 1948 showed that at least nine men of the "control" group who died of coronary heart disease at ages 45–64 were employed at one time as rayon process workers. Some of the excess of deaths in the controls when they were compared with the national figures conceivably could be accounted for by ex-rayon process workers.

There could be another explanation of the excess mortality from coronary heart disease among the rayon process workers —namely, that they are protected from *other* diseases and therefore have a higher proportional mortality from coronary heart disease (Morris, 1967) (see Chart). This seems unlikely, but the occupational risk of coronary heart disease, if there is one, can be proved only by direct measurements of actual death rates in a defined population of rayon workers. Eventually we found that such a study could be made in the most modern of the three factories reported on above. This is described next.

II. Death Rates in One Factory

The factory which started manufacturing rayon in 1935 kept detailed employment records which made it possible to identify and trace some 2,000 men and calculate appropriate death rates of those employed in the viscose making and spinning processes.

Methods

Choice of Population.—The population chosen comprised the men employed in the factory for one year or more at any time from 1 January 1945 to 31 December 1949. The analysis of mortality was confined to those aged 45 to 64 from 1 January 1950 to 31 December 1964. The number of men who were within these ages at any time during this 15-year period was 2,129. Almost a third were still employed in the factory in 1964 and from information already obtained in the first part of this investigation many of the rest were known to have died. Others were sought through the Central Register of the National Health Service. In all 1,980 (93%) were traced; 1,731 were alive and 249 dead by the end of 1964. Over 97% of those with more than 10 years' service in the industry were traced, and we are reporting only on them.

Occupational Classification.—For each of the men we obtained date of birth, dates of employment and occupations in the industry, and, where applicable, the date and certified cause of death. We next divided the men into three occupational groups: (1) process workers who had worked in the department making *viscose* but not in the spinning department; (2) process workers who had worked in the *spinning* department; and (3) *non-process* workers, including men who had spent less than one month in a process department. Men of foreman grade or higher were classified as "staff" and the remainder as operatives; the staff employed on process work cannot be subdivided into viscose and spinning groups, since most had worked in both as part of their training. Finally, we calculated for each of these occupational groups the number of man-years* lived at ages 45–49, 50–54, 55–59, and 60-64 during each of three quinquennial periods, 1950–4, 1955–9, and 1960–4.

Calculation of Death Rates.—We obtained all causes of death from death certificates and classified them as coronary heart disease, other cardiovascular disease, or other causes.† Knowing the man-years at risk in each age group in each quinquennial period it was possible to calculate the corresponding death rates per 1,000 man-years for these various rayon workers. The corresponding rates for the home population of England and Wales were calculated from the Registrar General's Tables. Thus the experience of the various occupations is first compared with the national experience. Later we compare the death rates in occupations within the factory.

Comparison with National Figures

Process Operatives.—The death rate from coronary heart disease of operatives in the viscose-making department was 2.2 against an expected rate of 3.2 per 1,000 man-years; they had 22 deaths from all causes against 28.5 expected (Table II). There is no evidence of an occupational mortality hazard in this department. The operatives in the spinning department with more than 10 years' employment had higher death rates than expected from coronary heart disease, other cardiovascular disease, and other causes. The death rate from coronary heart disease was 6.1 against 3.2 expected (Table II); this excess is highly significant ($P<0.001$); and all age groups over 50 contribute to it, particularly men aged 50–54 years. There are three sections in the spinning department—spinning itself, washing, and drying—and it is possible to get an indication of their relative risk by examining the mortality of men who spent at least 90% of their employed time in a particular section. Twice as many of the actual spinners died of coronary heart disease than expected (10 against 4.5, $P<0.01$). The excess among men in the washing section (5 observed against 2.2 expected) was similar but not significant; there was no excess in the drying section. These numbers are very small, but they do point to an occupational risk in the spinning section and possibly also in washing.

TABLE II.—*Observed and Expected* Deaths and Death Rates Among Operatives and Staff, Aged 45–64, with More than 10 Years' Employment in Rayon Factories*

Occupation	Man-Years at Risk	Coronary Heart Disease				Other Cardio-vascular Disease		Other Causes	
		Deaths		Rates per 1,000 Man-Years		Deaths		Deaths	
		O.	E.	O.	E.	O.	E.	O.	E.
Operatives:									
Viscose making ..	2,221	5	7·2	2·2	3·2	2	5·0	15	16·3
Viscose spinning ..	4,585	28	14·6‡	6·1	3·2	15	9·9	40	33·1
Non-process† ..	1,997	6	8·0	3·0	4·0	10	6·1	14	18·6
Staff:									
Spinning	1,502	9	4·3§	6·0	2·9	1	2·8	11	9·7
Non-process ..	752	3	2·3	4·0	3·0	2	1·6	3	5·2

* Expected figures are based on the national rates for England and Wales.
† Excludes 41 fitters.
‡ $\chi^2=12·2$; $P<0·001$.
§ $\chi^2=5·2$; $P<0·05$.

Non-process Operatives.—Two hundred and eighty-one non-process operatives with more than 10 years' employment in rayon factories showed no significant deviations from the expected mortality rates (Table II). Forty-one fitters have been excluded from this group because they had probably spent much of their time in the spinning department maintaining machinery. Six of them died of coronary heart disease against an expected number of 1.8.

Staff.—All but one of the 254 members of staff who were employed for more than 10 years were traced. Nine of the 163 who had service in the spinning department died of coronary heart disease, against 4.3 expected ($P<0.05$) (Table II).

* These calculations were based on whole years. So man-years have been slightly underestimated; but the error is small and can be ignored.

† All deaths were later classified independently by Dr. Margaret Crawand Dr. Barbara Womersley. There was about 95% agreement, with a slight underestimate of deaths from coronary heart disease by us.

Length of Service and Mortality Rate

The proportion of men traced was high enough in the spinning plus wash sections to assess also the mortality risk of those who had less than 10 years' employment. With 7 observed against 2.4 deaths expected from coronary heart disease ($P<0.01$) the occupational risk does not seem to be confined to men with long service.

Mortality in Spinning and other Departments

We have found, therefore, that compared with the national experience both operatives and staff in the spinning department with more than 10 years' employment had a significantly higher death rate than expected from coronary heart disease. By contrast, the men who had not worked in the spinning department had death rates from coronary heart disease lower than expected. Next, therefore, we compared directly the mortality of all men in the spinning and all men in other departments, by means of the death rates per 1,000 man-years, standardized for age and for year of death to allow for the secular changes in mortality.

These death rates from coronary heart disease are respectively 6.6 and 2.7 per 1,000 man-years for all men in the spinning-room and all men in other departments ($P<0.01$) (Table III). It is mostly accounted for by a significantly higher death rate from coronary heart disease in spinning-room operatives compared with other operatives. Men employed in the spinning-room showed also higher death rates for other cardiovascular diseases and from other causes, but the differences are not significant.

TABLE III.—*Standardized Death Rates Per 1,000 Man-Years for Staff and Operatives Aged 45–64 Years with More than 10 Years' Employment in Rayon Factories*

Occupation	Standardized Death Rates per 1,000 Man-Years*		
	Coronary Heart Disease	Other Cardiovascular Disease	Other Causes
Employed in spinning:			
Staff	7·1	0·9	9·0
Process operatives	6·4†	3·8	9·6
Total..	6·6‡	3·2	9·5
Not employed in spinning:			
Staff	4·4	3·2	4·6
Viscose operatives	2·3†	1·0	7·3
Non-process operatives§ ..	2·5†	4·1	6·0
Total..	2·7‡	2·8	6·3

* Standardized death rate = $\frac{\text{Observed deaths}}{\text{Expected deaths}}$ × crude death rate for males aged 45–64 in England and Wales for 1950–64.
† Normal deviate: 2·98. $P<0.01$.
‡ Normal deviate: 2·82. $P<0.01$.
§ Excludes fitters, many of whom are likely to have worked from time to time in the spinning department; their standardized death rate from coronary heart disease was 11·5 per 1,000 man-years.

CS_2 and H_2S Exposures

Routine monitoring for CS_2 and H_2S has been undertaken in this factory for at least 20 years, and the results of a fair sample of the tests made between 1946 and 1963 were available. Concentrations of CS_2 were lower in viscose-making than in spinning. In the viscose-making department 17% of tests in the churn rooms showed more than 20 p.p.m., the threshold limit value for CS_2 (Ministry of Labour, 1965). Exposure occurs almost entirely in the churn rooms, in which about a quarter of the viscose workers are employed at any one time; since many rotate their jobs, men spend most of their time in workrooms where there is no CS_2. Thus overall exposure was considerably lower than indicated by these figures. There is no exposure to H_2S in the viscose-making department.

In the spinning department nearly half of the sample tests showed more than the threshold limit value for CS_2. Exposures to H_2S were relatively low; few of the tests were above the threshold limit value of 10 p.p.m.

There are at least three possible explanations of an occupational risk of coronary heart disease occurring in the *spinning department* but not in the department making viscose; it could be caused by the higher exposures to CS_2 in the spinning department, or by exposures to H_2S which do not occur in viscose-making, or by the combination of the two.

To investigate whether or not CS_2 itself is producing the risk in the spinning-rooms, we recalculated the proportional mortality from coronary heart disease of men who worked *only* in the viscose-making departments of the three factories studied in Part I. The factory built in 1935 was equipped with modern churns, and their viscose-makers probably had much lower exposures to CS_2 than those in the other two factories. The men in the most modern factory had 6 observed and 5.0 expected deaths from coronary heart disease, whereas the men in the two older factories had 13 deaths against 4.6 expected. This supports the suggestion that exposure to CS_2 is a likely cause of the excess mortality in the spinning-room of the most modern factory, and that exposure of viscose makers in its churn room have been low enough not to constitute a mortality risk from coronary heart disease.

Discussion

We have identified an occupational risk in men exposed to CS_2 in three viscose rayon factories; there is evidence of a similar risk in a fourth factory in another county. Apart from the risk of angina pectoris and sudden death in workers exposed to nitroglycol and nitroglycerin reported by several workers and recently again by Lund, Häggendal, and Johnsson (1968) this seems to be the only "hard" evidence of an occupational toxic factor in the aetiology of ischaemic heart disease and related conditions.

Occupational hazards are often recognized without much difficulty. Thus industrial lead-poisoning or pneumoconiosis occur in limited groups of workers, present characteristic signs and symptoms, and the diagnosis may be confirmed by a biological test or specific *x*-ray changes. To identify a specific occupational risk of coronary heart disease is altogether another matter, because the disease is widespread among middle-aged men, and meanwhile nothing specific is known on the clinical presentation of the disease in this occupation. On present evidence there are multiple causes of coronary heart disease, and occupational exposure in viscose rayon manufacture appears to be another.

If CS_2 is in fact the responsible agent, discovery of its mode of action might help to clarify the aetiology of atherosclerosis and coronary heart disease, and such search should be related to the present interest in the role of trace elements in this disease (Crawford *et al.*, 1968). Several studies in other countries have already suggested a link between CS_2 exposure, lipid metabolism, and atherogenesis. High blood cholesterol levels have been reported in viscose rayon workers, with an increase usually in the β-lipoprotein fraction, but these have not been consistent findings (Brieger and Teisinger, 1967). Szendzikowski and Patelski (1962) found in rats that CS_2 reduced the lipolytic activity of the aorta in vitro and also the concentration of the non-esterified fatty acids in the plasma in vivo.

The first part of the present investigation showed that the excess of coronary deaths in the process workers did not occur before 1943, was highest in 1943–7, then fell gradually and was slight in 1958–62. The risk may therefore have arisen from wartime conditions and subsequently diminished with improving ventilation and the installation of modern churns. Furthermore, with reduced exposures to CS_2 in the churn

rooms, following improvements in methods of work, the risk seems to have been confined to the spinning-rooms. While the most likely agent is CS_2, the relatively low exposures to H_2S that occur in spinning-rooms cannot be dismissed.

Workers who may be exposed to CS_2 in the viscose rayon industry are periodically examined by the factory medical service. Prospective surveys now are also needed which could take into account several of the postulated causes and precursors of modern epidemic coronary heart disease, such as cigarette smoking, physical inactivity, and obesity. Serial blood lipid, blood pressure, and electrocardiographic observations should be made in such groups and in appropriate "controls." We would also like to see a detailed retrospective search of the clinical and necropsy reports of viscose rayon workers who have died of coronary heart disease for evidence of any special features of its natural history.

We cannot say whether men entering the viscose rayon industry today have an above-average risk of coronary heart disease. However, by examining the quantitative relationship between coronary heart disease mortality and the concentrations of CS_2 since 1945 it should be possible to decide whether there is any remaining mortality hazard and also to indicate the maximum concentration free of risk. The present threshold limit value for CS_2 of 20 p.p.m. relates only to its short-term toxic action and its acute systemic effects (American Conference of Governmental Industrial Hygienists, 1966), and is clearly an insufficient guide.

We are grateful to the rayon industry in the United Kingdom for making it possible to undertake this study; to the factory management and other specialized personnel for their help; and to Mr. Smale at the Central Register of the National Health Service and to the General Register Office for their valuable assistance in searching records. We would also like to thank members of the Department of Occupational Health and of the Medical Research Council's Social Medicine Research Unit for help and advice, in particular Miss Joan Walford, Miss Jane Cooper, Miss Rosemary Wood, Dr. Margaret Crawford, and Dr. Barbara Womersley. We are also grateful to Drs. Austin Heady, T. W. Meade, M. F. Oliver, and Michael Williams for help with the manuscript.

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Comparison of Side-effects of Tetracycline and Tetracycline plus Nystatin

Report to the Research Committee of the British Tuberculosis Association by the Clinical Trials Subcommittee*

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Summary: In a multicentre, double-blind, controlled trial of tetracycline plus nystatin (Mysteclin) and tetracycline, 111 patients with respiratory infections received one or other drug for a period of 10 days.

The incidence of gastrointestinal symptoms was high in both groups before treatment began, and somewhat higher in the Mysteclin group than in the tetracycline group. After 10 days' treatment 50% of the patients in the Mysteclin group had symptoms, a mean of 1.44 each, compared with 34% of the patients in the tetracycline group, with a mean of 1.47 symptoms each; the difference between the two groups is not significant ($P>0.05$). The incidence of Candida albicans in the stools at 10 days in the Mysteclin group (9.1%) was significantly lower than that in the tetracycline group (37.1%), but this was not reflected in any reduction in the frequency of gastrointestinal symptoms.

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The trial was co-ordinated by Dr. J. H. Angel and the mycology was done by Professor B. W. Lacey at the Westminster Medical School. The report was prepared by Dr J. H. Angel and Professor B. W. Lacey.

Introduction

Tetracycline is one of the most effective antibiotics for the treatment of respiratory infections, and especially for exacerbations of chronic bronchitis. It does, however, produce side-effects which manifest themselves most commonly in the gastrointestinal tract. There has been considerable disagreement about the frequency of these side-effects. Some authors (Childs, 1956; Chamberlain *et al.*, 1958; Larkin, 1959) have found them to be common, while others (Robinson, 1954) assert that they are rare.

It was originally thought that the gastrointestinal symptoms were due to deficiency of vitamins of the B complex following alterations in the gut flora. Later, however, it was suggested that they were related to overgrowth of fungi, and, in particular, of *Candida albicans*. Since nystatin is known to inhibit the growth of this organism it seemed logical to add it to preparations of tetracycline. The use of this combined tablet has been widely advocated, and has been recommended in some textbooks (MacLean, 1962; Murdoch, 1964). However, the cost of the combined tablet is higher than that of tetracycline alone. It seemed important to determine whether the addition of nystatin to tetracycline was justified. The Clinical Trials Subcommittee of the British Tuberculosis Association accord-