PAPERS AND SHORT REPORTS

Bladder tumours among rodent operatives handling ANTU

JOAN M DAVIES, H F THOMAS, D MANSON

Abstract

The rodenticide ANTU (alpha-naphthylthiourea) was used in the United Kingdom mainly in the late 1940s and early 1950s. The product then contained up to 0.2% of beta-naphthylamine as an impurity, and it was finally withdrawn in 1967 as a suspected carcinogen. Fourteen cases of urothelial tumours among rodent operatives exposed to ANTU are reported; in one district four out of 27 staff were affected, and in another area two out of 10. These cases strongly suggest that the early ANTU manufactured in the United Kingdom posed a cancer hazard to users.

ANTU is still made or used in various countries, though the current product may be relatively pure and no longer contaminated by beta-naphthylamine. Recent laboratory evidence shows that even pure ANTU is mutagenic in the Ames test, and the safety of this rodenticide may need review.

Introduction

In 1945 Richter¹ described the development of α -naphthylthiourea (1-[1-naphthyl]-2-thiourea), commonly termed ANTU, as a rodenticide in the United States. ANTU came into fairly widespread use in the United Kingdom in the late 1940s, generally as the rodenticide of third choice after arsenious oxide and zinc phosphide; its use declined after the use of warfarin became established in the early 1950s. Then (as now) most rodent operatives were employed by local authorities, though some worked for pest control firms, port health authorities, and railways. The Ministry of Agriculture, Fisheries, and

Food also employed staff to operate a service for farmers until the 1950s, when this service became purely advisory. ANTU was sold in the United Kingdom as an undiluted powder to be mixed with bait at a 2% concentration.² It was an "acute," single-dose poison effective against the common brown rat by inducing pulmonary oedema and pleural effusion.

ANTU was a reaction product of α -naphthylamine and thiocyanate salts,³ and some free unreacted naphthylamine remained as an impurity in the finished product. The commercial α -naphthylamine used in the 1940s and 1950s contained from 4% to 10% of β -naphthylamine as a contaminant,⁴ and consequently the impurity remaining in ANTU was likely to consist partly of β -naphthylamine, which is a potent bladder carcinogen. Indeed, it was already known in 1950 that some ANTU being manufactured in the United Kingdom contained up to 1% of unreacted naphthylamines, some of which would have been β -naphthylamine (R A M Case, personal communication). Later analyses of ANTU samples showed that in some cases β -naphthylamine formed up to one-fifth of the unreacted amines⁵—that is, about 0.2% of the ANTU—this high proportion probably resulting from preferential reaction of the alpha isomer in the synthesis of the rodenticide.

The first published mention of a possible risk of bladder cancer from the use of ANTU was by Williams in 1958,⁴ citing an observation by R A M Case. In 1959 the Ministry of Agriculture, Fisheries, and Food advised local authorities that ANTU should be used with caution, and only if warfarin resistance had occurred; as a result use of ANTU declined further. In 1965 the first known case of bladder cancer in a rodent operative exposed to ANTU was brought to notice by a medical officer of health and a clinician when Case mentioned the possible hazard in a lecture; early in 1966 a clinician elsewhere brought a similar case to notice. Both patients were able to claim industrial disease benefit on the grounds that they had been exposed at work to an officially recognised carcinogen.⁶ The Ministry of Agriculture, Fisheries, and Food was notified, and in 1966, on the advice of its advisory committee on pesticides, recommended that the use of ANTU should be suspended pending a review.⁵ Early in 1967 the Ministry advised that use should cease and that stocks should be destroyed.

Efforts were then made from the Institute of Cancer Research to ascertain how many other cases of bladder cancer had occurred amongst users of ANTU, but the findings were inconclusive. Recently a Cardiff-based survey of use of pesticides by local

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authorities was initiated,⁷ and data were pooled to make further searches for cases and to review the implications of the findings. No previous studies of bladder tumours after exposure to ANTU have been published.

Methods

In 1967 a systematic attempt was made to identify further possible cases of bladder tumour among rodent operatives exposed to ANTU by the use of death certificates. By courtesy of the Office of Population Censuses and Surveys, the Institute of Cancer Research received copies of all certificates for England and Wales mentioning bladder cancer or papilloma as a cause of death, and those for 1951 to 1965 (later to 1971) were scanned for men described as working in pest control. About half the 15 such cases found were specified to be local authority employees, and confidential inquiries were made to the relevant medical officers of health about their work histories and use of ANTU. Recently a further 13 possible cases during 1972-80 were identified, and these were confidentially investigated from Cardiff. This exploratory procedure could only yield case reports, since no data on the total numbers of employed or retired rodent operatives were available.

In 1966 the Ministry of Agriculture, Fisheries, and Food supplied the Institute of Cancer Research with confidential lists of some 275 former pest officers and operators employed by the Ministry who might have been in contact with ANTU. Ideally these lists might have constituted a useful nominal roll of exposed operatives, but in practice they were not comprehensive, some of the data were compiled from memory by current Ministry employees, and identifying details were scanty. The lists were checked originally against the death certificates for bladder tumour up to 1967, and recently up to 1980. The Ministry also supplied a list of old (before 1974) local authorities who reported using ANTU in 1964, when responding to a survey of pesticide usage.

For the Cardiff survey questionnaires were sent to all new (after 1974) local authorities in England and Wales, requesting dates of usage of particular pesticides (including ANTU), and lists of rodent operatives employed since 1946. A total of 79% of the authorities replied, and it appeared that at least 150 old (before 1974) districts had used ANTU. This figure probably understates the use of ANTU, however, for although some authorities had retained full records of both rodenticide usage and personnel ever since the second world war, most could provide data only from relatively recent dates or from the memory of staff still employed. A few reported use of ANTU starting or continuing at implausibly late dates, and there were discrepancies with the Ministry of Agriculture, Fisheries, and Food's list of users in 1964. The data on employees were also of variable quality, and dates of birth or ages were not always supplied. The early (main) period of use of ANTU was not always covered, and it is uncertain whether selection biases would have favoured the inclusion or exclusion of deceased workers. Thus, this source also failed to provide an unbiased nominal roll of workers exposed to ANTU, though 360 men were listed as possible handlers of ANTU and had identification details adequate for checking against the death certificates for 1951-80.

Because of the incompleteness and selection biases of both the Ministry and local authority lists no attempt was made to calculate precise "expected" numbers of deaths from bladder tumours at national rates for either group.

There were, however, three small subgroups of workers exposed to ANTU on the local authority lists that appeared complete and unbiased, and which merited more detailed study. The district where the first known case had occurred (district 3) provided a reliable and detailed list of all 27 male employees exposed to ANTU, and was within the area of a cancer registry with good coverage of local cases of bladder tumour (including papillomas) since at least 1961; a second death from bladder cancer had already come to light, and the registry searched their 1961-80 records for any further cases among the remaining 24 men (one man having died from other causes before 1961). Another district (6) also had good records, and current staff had kept contact with past workers; here also two deaths from bladder cancer had come to notice, among a total of 10 men exposed to ANTU, and a check was made for further cases among the other eight. The third group comprised 19 men employed at relevant dates by the 12 districts using ANTU in the area covered by another cancer registry with reliable coverage (including bladder papillomas) from 1961. The 12 districts were all small, but their records appeared good, and only one other man on their lists had to be omitted for lack of adequate identifying details.

For all three groups (totalling 51 men, excluding four known cases) the numbers of registered cases of cancer of the bladder, renal pelvis, ureter, urethra, and urachus, and of benign bladder tumours were compared during 1961-80 with the numbers expected, using specially compiled national registration rates. These rates were compiled in five-year age groups for the periods 1962-5 (used for 1961-5), 1966-70, 1971-5, and 1976-7 (used for 1976-80), from published numbers of registrations for England and Wales⁸⁻¹⁰; interpolations were made for minor sites where numbers were given only for 10-year age groups. Non-malignant bladder tumours were not registered nationally before 1971, and cancers of the renal pelvis and ureter were not distinguished before 1965; for both groups numbers were estimated on the basis of the first few years of known experience. The significance of the excess of observed over expected cases was measured assuming a Poisson distribution, using a one-tail test. This comparison of observed and expected registered cases was somewhat biased against obtaining an excess of observed cases, for previously known deaths in districts 3 and 6 were excluded, recent checks of death certificates had not revealed any more cases, and none had been known to local authority staff preparing their lists for Cardiff. Moreover, the estimated expected numbers of cases would have been slightly exaggerated by assuming that 13 untraced men were alive through 1980 and that three men of uncertain age were aged 65 when they left employment; the national registration rates used were similar to or slightly higher than those of the two cancer registries.

Results

Table I gives dates and ages at death for the 28 men found by systematically searching death certificates of men who had died of bladder tumour for those described as working in pest control, and shows the results of attempting to ascertain their work histories.

TABLE I—Men dying with bladder tumours during 1951-80, who were described on their death certificates as working in pest control*

Dates	No of cases	Age at death			Case No and detail
		No information received	Use of ANTU excluded or unlikely	Use of ANTU confirmed	
1951-5	None				
1956-60	2	63	73†		
1961-5	7		62, 62, 72† 77, 83	69	1. District 1. Rodent operator 1944-52. No details of ANTU use
				58	2. District 2. Rodent operator 1951-64. Limited use of ANTU
1966-70	6	62	47, 53, 72, 86	77	3. Ministry pest officer, about 1946-60. No details of use of ANTU
1971-5	9	67, 78†, 79, 83	66, 68, 71, 73	87	4. Ministry pest officer, late 1940s-58. Used ANTU until about 1951
1976-80	4	68†, 69, 77, 78			
Total	28	10	14	4	

* Excludes four cases (5, 6, 9, 10; see table II) ascertained before death.

† Bladder cancer mentioned only as a contributory cause of death.

Adequate information was obtained in 18 cases. When the first check up to 1965 was made two men were found to have handled ANTU recently two more such cases were found (3, 4), but for case 3 the exposure may have been quite slight. Cases 5, 6, 9, and 10 (table II) were brought to notice before death, but would have been found later from their death certificates.

No deaths from bladder tumour were found from the check of 275 employees on the Ministry of Agriculture, Fisheries, and Food lists. The two Ministry workers shown in table I did not feature on the lists confirming the incompleteness of these. The 83-year-old man dying in the 1971-5 period may also have worked for the Ministry, but this remains unconfirmed. The search for deaths among the 360 rodent operatives exposed to ANTU listed by local authorities revealed only four cases already known from other sources (5, 6, 8, 10); had this

TABLE II—Cases of urothelial tumour among rodent operatives who used ANTU, ascertained among patients still living

Case No	Date of onset	Age at onset	Year of death	Source of information	Employment as rodent operatives	
					Dates and districts	Use of ANTU
5*	1957	73	1975	Medical officer of health and clinician	1944-60 District 3	ANTU was used from late 1950 to 1963; mixed and laid bait
6*	About 1965	66	1966	Hospital clinician	1950-66 District 5	Reported to have mixed and laid ANTU bait six times
7	1959	44		Routine hospital interview	1947-59 District 4	Used ANTU experimentally only, and had previous exposure to carcinogens elsewhere
8*†	1969	65	1972	Medical officer of health	1951-67 District 3	ANTU was used from late 1950 to 1963; mixed and laid bait
9*	1971	66	1974	Hospital clinician	Exact dates not known District 6	ANTU was used from about 1950 to 1959; mixed and laid bait, but duration of contact not known
10*	About 1972	72	1972	Medical officer of health	1947-62 District 6	ANTU was used from about 1950 to 1959; mixed bait
11	About 1980	64		Local authority	1955-80 District 8	Use of ANTU very slight, and had previous exposure to carcinogens
12	1975	72		Cancer registry	1950-68 District 3	ANTU was used from late 1950 to 1963; mixed and laid bait
13‡	1976	76	1976	Cancer registry	1932-67 District 3	ANTU was used from late 1950 to 1963; mixed and laid bait
14	1979	63	1979	Cancer registry	1946-70 District 7	ANTU was used from 1950 to 1954; extent of contact not known

* Died with a bladder tumour as main or contributory cause.

† Not specified on death certificate as working in pest control.

‡ Cancer of the ureter.

source alone been used, the deaths of cases 1, 2, and 9 would have been missed. In addition, one local authority reported a current employee to have been treated for a bladder tumour (11), but this man had had only slight exposure to ANTU and his tumour was probably attributable to earlier exposure to carcinogens in a chemical factory.

Table II lists all 10 cases of urothelial tumour that were ascertained among living patients. Cases 5, 6, 8, 9, and 10 were brought to notice by medical officers of health and clinicians; case 7 was found by routine hospital interview, and was the youngest affected case, but as with case 11 his use of ANTU was very slight and he had prior exposure to carcinogens in a cable factory. Cases 12, 13, and 14 were found in the searches of the cancer registry, which revealed these hitherto unknown cases among the three subgroups of 51 exposed operatives (table III).

TABLE III—Observed and expected cases of urothelial tumour registered from 1961 to 1980 among 51 rodent operatives exposed to ANTU

District	No of men	Estimated man-years	Observed cases	Expected cases
District 3	24	421	2*	0.23
District 6	8	149	0	0.09
Districts 3 and 6	32	570	2*	0.32
Twelve small districts	19	347	1	0.28
Total	51	917	3*	0.60

* $p < 0.05$.

Despite the small numbers there are significant excesses of cases for district 3, districts 3 and 6 combined, and all subgroups combined, at the 5% level of significance. Case 12 is still living; case 13 died from other causes soon after his cancer of the ureter was diagnosed; case 14 was already noted on the local authority list to have died from cancer of the larynx in 1979, but it had not been known that he also had a bladder cancer diagnosed in that year. Neither case 13 nor case 14 had urothelial cancer mentioned on their death certificates.

Discussion

As a method of case finding the use of death certificates has obvious limitations; cases may be missed because the disease has not caused death or because men have ceased to be rodent operatives and are otherwise described at death. The fact that this method revealed cases that would not have been found from use of the nominal rolls supplied by the Ministry of Agriculture, Fisheries, and Food and the local authorities indicates how fallible those rolls were because of the inadequate records

remaining from the main early period of use of ANTU. Because of incomplete data the true total of cases of bladder tumour among rodent operatives exposed to ANTU will never be known.

In the late 1960s there was little indication of a widespread excess of bladder tumours among users of ANTU: only five cases possibly attributable to ANTU were known (cases 1, 2, 5, 6, and 7), and the Ministry list revealed no other deaths. The possible risk had been publicised in the United Kingdom, and the product withdrawn. Subsequently cases 3, 8, 9, and 10 came to notice, and the presence of two cases at both districts 3 and 6 strengthened the suspicion that exposure to ANTU posed a hazard. Nevertheless, the possibility of two such pairs of cases occurring by chance among all the districts using ANTU could not be entirely ruled out, for urothelial tumours are fairly common: at present rates a man's cumulative risk of developing such a tumour up to age 75 is over 1 in 50. The most convincing evidence against ANTU is therefore the significant excess of additional cases found among the 51 operatives checked against the records of the cancer registries. In particular it is very unlikely to be a chance finding that two further cases were found at district 3, bringing the total there to four men affected out of only 27. The study findings for districts 3 and 6 and the 12 small districts suggest strongly that the early ANTU used in the United Kingdom was carcinogenic.

Information is available about use of ANTU in districts 3 and 6 from records and from recollections of staff employed in the 1950s. District 3 is a large urban area, and ANTU was used in the refuse destructors and the sewers from late 1950 until 1963, with use highest in 1951-3 and slight after 1959. Records show that there were 95 ANTU treatments in 1951, though as little as 7 g or 14 g ($\frac{1}{4}$ or $\frac{1}{2}$ oz) was used in some treatments, and the total amount of ANTU bought after 1951 was probably about 18 kg (40 lb). District 6 is mainly rural, and it is reported that up to 23 kg (50 lb) of ANTU were used on farms annually in the early 1950s; the use of ANTU was abandoned in about 1959.

In each district the operators who laid the poisoned bait also prepared it, mixing one part of ANTU with about 50 parts of sausage rusk or cereal. The bait was usually wet, but was mixed dry for some treatments. The mixing was done by hand in the early years of use, with a small handfork or a shovel; in one district it was done in a very small room, and in the other in a cellar. The mixing produced a fine airborne dust that would have been inhaled, and there would also have been absorption of dust or caked material through the skin; one informant recalled that the mixing caused short-term respiratory symptoms if it was continued for too long at a time. Exposure during the subsequent laying of the poisoned bait was probably much less. All six affected men are known to have mixed bait, and the intervals between their first exposure to ANTU and the diagnosis of their

tumours were about six years for case 5, and 18, 20, 21, 24, and 25 years respectively for cases 8, 9, 10, 12, and 13: except in case 5 these are typical latent periods for occupational bladder cancers.

Though there have probably been cases of bladder tumour elsewhere in the country that have not come to light, districts 3 and 6 appear to have a disproportionate number of cases. Possibly their staff handled more ANTU and mixed it under poorer conditions than elsewhere, but this remains a speculation. We know little about early use in other districts, for first-hand information about practice 30 or more years ago is very difficult to obtain.

In the United States extensive field trials of ANTU were carried out during 1942-5 in residential areas of the city of Baltimore: over 1500 volunteers, including boy scouts, applied ANTU treatments in heavily populated blocks, and "more than 500 000 residents" came "in contact either with the poison as such or with poisoned baits."¹ It appears very likely that this early ANTU would have been contaminated by β -naphthylamine, and that a substantial proportion of the wartime population of Baltimore was thereby inadvertently exposed to a carcinogen. Even though exposures were probably very slight in most cases, especially compared with those of rodent operatives in the United Kingdom, it would be of considerable interest to know whether the later incidence of bladder tumours among Baltimore residents or among staff of the city rodent control office gives any indication that the field trials of ANTU created a cancer hazard. At the Institute of Cancer Research Chilvers¹¹ studied cancer mortality in Baltimore and 19 other large American cities in connection with the fluoridation of water supplies, and has calculated standardised mortality ratios for cancers of the bladder and kidney combined in Baltimore at certain dates, for both sexes at all ages. These calculations use American national rates for 1960 and 1970, with simultaneous indirect standardisation for sex, age, and race. The standardised mortality ratio for 1958-62 is 142 (based on 464 deaths), compared with a mean of 120 for all 20 cities. For 1968-72 the standardised mortality ratio in Baltimore is 114 (based on 394 deaths), compared with a mean of 112 in all 20 cities. During 1963-7 there were 423 deaths, but reliable population data are not available for the calculation of expected numbers.

The most likely explanation for the carcinogenicity of the ANTU used in the United Kingdom appears to be its β -naphthylamine impurity of about 0.2%, similar to that in the rubber anti-oxidant Nonox S, which was a potent bladder carcinogen.^{4, 12} Though exposure to ANTU was generally less severe than industrial exposures to Nonox S, the rodenticide was handled under unfavourable conditions in districts 3 and 6. Moreover, in addition to the risk from the impurity, it is possible that the absorption of ANTU might result in some β -naphthylamine being formed in vivo by the metabolism of 1-(2-naphthyl)-2-thiourea, which would be present in the product as a result of the method of synthesis. Scheline *et al*¹³ found that the related product 1-phenyl-2-thiourea yielded aniline as a urinary metabolite in rats and rabbits, and Lee *et al*¹⁴ found that ANTU was metabolised to 1-naphthylurea by rat liver and lung microsomes.

What of the ANTU still used today in various countries? If still made from α -naphthylamine contaminated by β -naphthylamine it must be assumed to be carcinogenic, but the current product may be made from pure α -naphthylamine and thiocyanate salts. Such ANTU will be free from β -naphthylamine, but will probably still contain some unreacted α -naphthylamine. Even if ANTU is made by the alternative method using 1-naphthyl isothiocyanate and ethanolic ammonia³ there may still be some unreacted amine, since the former substance is commonly prepared from α -naphthylamine. Alpha-naphthylamine might also be formed in vivo from ANTU. There is no clear epidemiological evidence to show whether or not pure α -naphthylamine is carcinogenic in man,¹⁵ though recent experiments show that it is non-carcinogenic or only weakly carcinogenic in dogs.^{15, 16} One must also consider the possibility that pure (naphthylamine-free) ANTU itself, or its metabolites, might be carcinogenic. It

has been suggested that the carcinogenicity of Nonox S was disproportionate to its slight β -naphthylamine impurity, and that the finished product itself might be dangerous^{12, 17}; the same possibility might be raised for ANTU. Kawalek *et al*¹⁸ have shown that pure ANTU is mutagenic in the Ames test, though only in the presence of a liver supernatant; they have also found that it transforms hamster embryo cells in an in-vitro test. These observations suggest that independent of any naphthylamine content ANTU might have carcinogenic potential through metabolic activation. The rodenticide has been little tested for carcinogenicity in animals, but in the United States Innes *et al*¹⁹ found no significant indication of tumorigenicity after oral administration of commercial ANTU to mice.

We do not know the extent of recent and current use of ANTU in other countries, nor whether it declined after the World Health Organisation advised against its use in 1973.²⁰ In the United States several firms were marketing ANTU around 1970 (Environmental Protection Agency, personal communication), and a 1979 text²¹ described it as "a rodenticide used extensively." The 1966 British warning⁵ about ANTU's possible carcinogenicity was noted in France,²² but elsewhere appears to have attracted little attention. Recent toxicology texts in the United States^{21, 23} and even the official American *Occupational Health Guideline for ANTU*, drawn up in 1978,²⁴ report the acute toxic hazards of ANTU use, but make no mention of possible carcinogenicity.

It is our opinion that early ANTU was carcinogenic, and that judgment should be reserved about the safety of the current product.

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Requests for reprints to Dr J M Davies.

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Bronchiolectasis—a complication of artificial ventilation

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Abstract

Pulmonary barotrauma associated with artificial ventilation is recognised clinically as pneumothorax, pneumomediastinum, or subcutaneous emphysema. Eleven patients who died in the intensive therapy unit after artificial ventilation were found at necropsy to have pronounced bronchiolectasis, which was associated with a greatly increased physiological dead space during life. The condition was best predicted by the maximum level of positive end expiratory pressure and the duration of application of positive end expiratory pressure. The clinical course of the lesion in survivors is not known.

Further detailed studies are needed, but it is suggested that high levels of positive end expiratory pressure should be used with caution.

Introduction

The lungs may be damaged by artificial ventilation with intermittent positive airway pressure. Pulmonary barotrauma from this cause has been defined as the development of pneumothorax, pneumomediastinum, or subcutaneous emphysema,¹ to which has been added tension lung cyst² and hyperinflation of a lung or lobe.³ The incidence of the first three conditions is 10% and the use of positive end expiratory pressure up to 1 kPa has been claimed not to increase the risk.¹ More recently, Cullen and Caldera⁴ reported a much lower incidence of these forms of pulmonary barotrauma, which can be causally related to artificial ventilation.

Such definitions of pulmonary barotrauma may be too restricted, however, and we have recently observed at necropsy a pronounced dilatation of terminal and respiratory bronchioles,

producing a condition like honeycomb lung in patients who were artificially ventilated and in whom high levels of airway pressure were used. The histological appearances will be described in detail elsewhere. We have attempted in this paper to determine the relation of bronchiolectasis to the circumstances of artificial ventilation.

Materials and methods

Patients—The study was retrospective and based on 11 consecutive necropsies of patients who died in the intensive therapy unit after artificial ventilation. No patients were excluded. All except case 3 (inactive pulmonary tuberculosis with fibrosis of both upper lobes) were free of appreciable primary pulmonary disease on admission to hospital but subsequently required artificial ventilation for respiratory failure associated with the causes listed in table I. In most cases, pulmonary complications developed before or during artificial ventilation such that intrapulmonary shunting (10-60%) required an increase in the inspired oxygen concentration (over 95% in four cases). Positive end expiratory pressure (0.4-2.3 kPa) was used in seven patients.

Pathology studies—At necropsy the lungs were fixed in inflation either by gaseous formaldehyde⁵ or, in two cases, by instillation of liquid formalin. The maximum inflation pressure using gaseous formaldehyde was 3 kPa. After fixation the lungs were examined macroscopically and cut into 1 cm slices. Multiple blocks (average 12 blocks/case) were taken from each lung and 4 μ m paraffin sections were stained with haematoxylin and eosin. Selected blocks were stained with connective tissue stains. Each section was examined independently by two pathologists, both unaware of the duration and manner of artificial ventilation carried out during life. The degree of bronchiolectasis was assessed semiquantitatively on a scale 0 (normal) to 4 and the views of the two observers aggregated by summation of the individual scores to give an aggregate score ranging from 0 to 8. In no case did individual assessments of the same patient differ by more than one grade and in nine cases the scores were identical.

Statistics—The bronchiolectasis score was related to variables characterising the circumstances of the artificial ventilation using stepwise multiple regression analysis and Kendall's rank correlation.

Relation of bronchiolectasis to pulmonary dead space—Formal measurement of pulmonary physiological dead space was not undertaken during artificial ventilation but an approximate and indirect estimate of the ratio of dead space to tidal volume (V_D/V_T) is provided by the product of minute volume and arterial P_{CO_2} (1 kPa), which equals CO_2 production (ml/min) $\times 0.1/(1 - V_D/V_T)$. To allow for variations in CO_2 production, we standardised the product for body weight, age, sex, and body temperature. The normal value for the

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