Discussion

R.S.V. was first found in human beings by Chanock *et al.* (1957), who isolated it from two children with pneumonia. Since then its association with many cases of bronchiolitis has been shown by workers in America, and Peacock and Clarke (1961) have recorded its isolation from two cases in this country.

To ensure isolation, specimens should not be frozen before being cultured, and a special strain of tissue culture cells known to be sensitive to R.S.V. must be used. These factors would account for failure to isolate it from the infants in the Birmingham outbreak of 1956-7. All specimens were frozen several times before they were put on to tissue cultures and those used were probably insensitive to R.S.V. But the fact that 68.7% of the 32 convalescent sera tested have shown significant, and mostly very considerable, rises in complement-fixing antibody to R.S.V. indicates that it was the primary cause of the bronchiolitis in the majority of the infants in this outbreak.

As might be expected, better serological responses were given by the older infants, though one only 2 months old attained a titre of 1/256. The reactions shown by the infant of 3 weeks with titres of 1/16 in both sera must have been due to maternal antibody, as were possibly those shown by the two with titres of 1/4 and 1/8 in their paired sera; otherwise this common difficulty in interpreting serological reactions in the very young was refreshingly absent.

Respiratory infection, often of the common-cold type, is frequently present in other members of the household when an infant goes down with bronchiolitis. R.S.V. in older children and adults, many of whom have demonstrable antibodies, usually produces a common-cold type of infection. It is possible that further investigation of winter respiratory infections will show that epidemics of infantile bronchiolitis occur when the prevailing virus in the general population is R.S.V., while the sporadic cases may be associated with other types of respiratory virus.

Summary

Stored sera collected during an investigation of epidemic infantile bronchiolitis in 1956-7 have been investigated for evidence of respiratory syncytial virus infection. The original investigation had failed to show any evidence of a virological cause for the condition.

Out of 32 pairs of sera tested for complement-fixing antibodies to respiratory syncytial virus, 22 have been found to show significant rises of titre.

Thus it is shown that respiratory syncytial virus must have been the main aetiological factor in the outbreak.

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The 1962 New Zealand health stamps (1d. from the sale of each stamp is diverted to the maintenance of health camps for children) were placed on sale on October 3. The stamps depict New Zealand birds in their natural colours. The 3½d. denomination shows the kakariki (parakeet) and the 4d. denomination the tieke (saddleback).

ADULT LEUKAEMIAS AND DIAGNOSTIC X RAYS

BY

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The present investigation was designed to detect possible associations between exposure to medical x rays and the subsequent development of malignant diseases in adults, and was modelled on a recent survey of childhood cancers (Stewart, Webb, and Hewitt, 1958).

Method

The earlier survey was restricted to children under 10 years who died between 1953 and 1955, and histories were obtained from parents. The adult survey was restricted to men and women over 20 years of age who were in hospital during 1958-60, and histories were obtained by interviewing patients. On both occasions the survey populations were recruited on a national basis and interviewed on a regional basis; cases and controls were matched for age, sex, and district, and data were collected by medical officers of health (survey doctors). The effects of observer error were randomized by an arrangement which ensured that each interviewer contributed an equal amount to case and control data.

In the childhood survey, leukaemias and cancers were notified by the General Register Office, and each dead child was matched with a live child of the same age and sex who was born in the same district. Both parents were interviewed by the same doctor (case/control pairs), and controls were obtained by asking clerks in charge of local birth registers to compile "short lists" of possible controls (that is, live births with the necessary matching characteristics).

In the adult survey, only leukaemias and lymphosarcomas were notified in the first instance. Details of these cases were supplied by hospital consultants who also undertook to find cancer patients of the same age and sex in the same or near-by hospitals. These "case pairs" were converted into "survey trios" by the addition of healthy controls, who were obtained by asking clerks to local executive councils to compile short lists of possible controls from local registers of N.H.S. patients. Survey trios in different regions were interviewed by different doctors, but each member of a given trio was seen by the same doctor. The leukaemia classification was based on pathologists' reports, copies of which were included in the survey data.

X-ray Data

Survey records of x-ray exposures and illnesses were confined to events which occurred during adult life and preceded the malignant disease (cases) or equivalent date for controls. These so-called *closing dates* marked the onset of symptoms and corresponded to "onset dates" in the childhood survey. For each x-ray attendance

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the following particulars were recorded: date, reason, type of treatment or investigation, parts of body exposed, probable number of exposures, and name of hospital.

Hospitals had usually kept radiotherapy records which stated how many times the patients had been treated (x rays) or how long the tissues had been exposed (radium implants). Attempts to discover exact numbers of diagnostic exposures from hospital records were less successful, and for these it was rarely possible to do more than check the date, reason, and nature of the investigation.

It was decided, therefore, to equate therapeutic x rays with numbers of treatments or "exposure days," and to give standard scores to standard diagnostic procedures (see Table I). These scores were decided by a radio-

TABLE I.—Standard Ratings for X-ray Investigations

X-ray Investigation	Standard Ratings (Estimated Number of Exposures)
Barium meal with follow-through	11
Tomograms	10
Proved fractures of long bones	8
Barium meals	7
Intravenous pyelograms	6
Barium enemas	4
Cholecystograms	3
Barium swallows	3
Salpingograms	2
Bronchograms	2
Obstetric x-ray examinations	2

logist, who based them on average numbers of exposures (films or screenings) in his department. Diagnostic x-ray exposures which did not fall into these categories were scored according to the number of films as stated by the patient, and therapeutic x-ray exposures which could not be traced were given the average number of treatments for the given condition.

Therapeutic and diagnostic scores were computed separately for x-ray exposures of the chest and abdomen (trunk exposures) and other x-ray exposures (peripheral x-ray exposures), and intervals between x-ray attendances and closing dates were calculated. These intervals were measured in calendar years; x-ray exposures recorded during the same year as the closing date were allocated to the preceding year, and if an x-ray attendance could not be precisely dated the score was divided equally between the possible years.

Prevalence rates for x-ray exposures were based on numbers of individuals reporting trunk and peripheral x-ray exposures in stated periods, and exposure rates on numbers of x-ray treatments or diagnostic x-ray exposures in stated periods. To avoid confusion between therapeutic and diagnostic x-ray exposures, all cases and controls with radiotherapy histories were excluded from the later analysis of diagnostic x-ray exposures. In the following account the terms "first quinquennium," "second quinquennium," "first decade," etc., will sometimes be used to describe five- and ten-year periods before closing dates.

Survey Population

By the end of 1961 there were records for 906 complete trios and 117 sets which lacked either a cancer case (68) or a healthy control (45) or both (4) (see Table II). A wide range of malignant diseases was included among the cancers, and only the following were represented by more than 50 cases: breast (191); large intestine and rectum (96); lung (92); skin (78); uterus (74). The leukaemias included the following cell

types: lymphatic (452); myeloid (450); lymphosarcomas (60); monocytic (41); and other or unspecified (20). Since there were approximately 7,500 adult deaths from leukaemia during 1958–60 in England and Wales, the survey population probably included an eighth of the available cases.

TABLE II.—Survey Population: Complete and Incomplete Trios

	Leukaemias	Cancers	Controls
Complete trios	906	906	906
Incomplete sets	45 68 4	45 — —	— 68 —
Total	1,023	951	974

In the statistical analyses the original cancer group was always treated as a single entity, but the original leukaemia group was divided into two halves (see Table III). The so-called L series included 512 lymphatic leukaemias and lymphosarcomas, and the so-called M series the remaining 511 cases. Most of the leukaemias were chronic cases, but there were 78 acute and subacute cases in the L series and 196 in the M series. There were also more men in the L series

TABLE III.—Survey Population: Diagnostic Subgroups

Diagnostic Groups		Nos.	Males %	Under 50 Years %
L series (16)	Lymphatic leukaemias ..	452	59	18
	Lymphosarcomas ..	60		
M series (28)	Myeloid leukaemias ..	450	42	45
	Monocytic ..	41		
	Other and unspecified leukaemias ..	20		
Leukaemias (44)		1,023	52	23
Cancers (18)		951	51	30
Controls (18)		974	51	30
Total (80)		2,948		

Figures in parentheses indicate persons with radiotherapy histories.

(59%) than in the M series (42%) and more cases under 50 years in the M series (45%) than in the L series (18%).

It so happened that therapeutic x-ray exposures were relatively common among women and old patients, and diagnostic x-ray exposures were relatively common among men and young patients. Consequently, differences between L and M series leukaemias in respect of age and sex have not distorted the x-ray findings as much as might be expected. This is shown by the fact that prevalence rates and exposure rates which ignored age and sex differences (crude rates) were almost the same as the rates which were obtained after standardizing for age and sex differences (standardized rates). All expectations have been standardized, but much the same results would have been obtained if this precaution had not been taken.

In the preliminary analyses four types of leukaemia were given separate consideration (lymphatic, myeloid, lymphosarcomas, and others) and the 906 cases belonging to complete trios were kept separate from the 117 cases belonging to incomplete sets. The final merging of all leukaemia cases into two groups was done in order to strengthen numbers, after it had been established that the incomplete sets made no difference to the results, and that there were no significant differences between lymphatic leukaemias and lymphosarcomas.

Condition at Time of Interview

There was, of course, no possibility of the cases and controls being alike from the point of view of general fitness to answer questions. It was also possible that patients in private wards were under-represented in the survey population, and that attitudes towards the interviews would be different for cases and controls. To check these points survey doctors were asked to record a number of facts which are summarized in Table IV. The figures in this table show that there were considerable differences between cases and controls (but very little difference between the three case groups) in respect of social class, physical and mental state at the time of the interview, and attitude towards the interview. It is not possible to say how far these

TABLE IV.—*Social Class and Condition at Time of Interview*

	Case Groups			Controls (%)
	M Series (%)	L Series (%)	Cancers (%)	
Co-operativeness:				
Good	95.5	94.3	94.7	97.2
Fair	3.0	4.7	3.7	2.6
Poor	1.5	1.0	1.6	0.2
Physical state:				
Good	35.8	47.6	57.2	85.1
Fair	50.7	43.9	39.7	14.3
Poor	13.5	8.5	3.1	0.6
Mental state:				
Good	84.6	84.4	88.3	94.8
Fair	14.3	13.8	10.3	5.0
Poor	1.1	1.8	1.4	0.2
Social class:				
I and II ..	17.5	20.1	19.9	25.9
III	58.4	59.2	56.1	56.0
IV and V ..	24.1	20.7	24.0	18.1

differences have affected the x-ray records, but the controls were, as a group, more alert and co-operative than the cases. They might therefore be expected, for this reason alone, to recollect a higher proportion of the x rays that they had experienced than the cases.

Radiotherapy

In the survey population as a whole there were 51 women and 29 men with histories of radiotherapy, 62 of whom were over 50 years of age at the time of the closing dates (see Table V). Twenty-four of these patients were treated for skin complaints, 23 for gynaecological disorders, and 20 for rodent ulcers or

TABLE V.—*Age-and-sex Distribution of Survey Population*

	Case Groups				Controls	Survey Population
	M Series		L Series	Cancers		
	A/M*	C/M†				
Males:						
<40 ..	24	23 (1)	22	61	64	194 (1)
40-49 ..	21 (2)	23 (2)	39 (1)	77 (2)	86 (1)	246 (8)
50-59 ..	16	34	94 (2)	132 (4)	139 (5)	415 (11)
60-69 ..	26	24 (2)	95 (3)	143 (1)	135 (1)	423 (7)
70+ ..	8	11	48	64 (2)	65	196 (2)
Total	95 (2)	115 (5)	298 (6)	477 (9)	489 (7)	1,474 (29)
Females:						
<40 ..	17 (1)	41	10	57	64 (3)	189 (4)
40-49 ..	16	48 (3)	17 (1)	74 (1)	75	230 (5)
50-59 ..	18 (5)	37 (5)	52 (3)	115 (3)	113 (5)	335 (21)
60-69 ..	26 (3)	46 (3)	79 (4)	137 (5)	154 (2)	442 (17)
70+ ..	13	11 (1)	40 (2)	73	61 (1)	198 (4)
Total	90 (9)	183 (12)	198 (10)	456 (9)	467 (11)	1,394 (51)
Both sexes	185 (11)	298 (17)	496 (16)	933 (18)	956 (18)	2,868 (80)

Figures in parentheses indicate subjects with histories of radiotherapy (not included in main figures).

* A/M = Acute and subacute cases. † C/M = Chronic and unspecified cases.

suspected cancers (see Table VI). There were 10 patients whose treatments necessitated exposure of the trunk and limbs; 43 who had only the trunk exposed; and 27 who only had peripheral exposures. Twelve records of remote exposures (that is, more than 10 years before the closing dates) could not be traced, 8 of which probably related to a single exposure for dermatitis of the hands or feet.

TABLE VI.—*Reasons for Radiotherapy*

		Radiotherapy Procedures			
		X Rays	Radium	Other*	Total
Reasons	Dermatology ..	23	—	1	24
	Artificial menopause ..	10	13	—	23
	Suspect cancers ..	10	2	—	12
	Rodent ulcers ..	5	3	—	8
	Spondylitis ..	6	—	—	6
	Other ..	5	1	1	7
Hospital records	Found ..	48	18	2	68
	Lost ..	11	1	—	12
Exposure sites	Trunk ..	29	14	—	43
	Periphery ..	23	4	—	27
	Both ..	7	1	2	10
Totals ..		59	19	2	80

* Radioactive phosphorus (1) and thorium (1).

The 37 subjects who had peripheral exposures were evenly distributed between case and control groups, but the 53 subjects with trunk exposures were concentrated among M series leukaemias (see Table VII). In this group the expected number of trunk exposures (that is, the standard set by the whole population) was 9.2 and the observed 24. For all other subjects the expected and observed numbers were 43.8 and 29 respectively.

Exposure rates for therapeutic x rays are shown in Table VIII. During the three years immediately preceding the closing dates the M series rate for trunk exposures (8.28) was 33 times higher than the rate for other subjects (0.25) and still higher after standardization (34.8 times). Differences were less marked for more remote exposures, and for trunk x-ray exposures more than 20 years before the closing dates the rates

TABLE VII.—*Radiotherapy Prevalence. Observed and Expected Numbers for Cases and Controls*

Diagnostic Groups	Prevalence (i.e., Affected Persons)				Total (Persons)
	Trunk Exposures		Peripheral Exposures		
	Observed	Expected	Observed	Expected	
M series ..	24	9.2	8	6.4	28
L	9	9.1	7	6.4	16
Cancers ..	10	17.2	11	11.9	18
Controls ..	10	17.5	11	12.2	18
Total	53		37		80

Figures in italics in this and subsequent tables are significantly higher than standard (that is, whole population).

TABLE VIII.—*Radiotherapy Exposure Rates (×100) (Mean Annual Estimations. See Text)*

Year to Closing Dates	Trunk Exposures		Peripheral Exposures		Ratio† M Series: Standard Group Trunk Exposures
	M Series	Standard Group*	M Series	Standard Group	
1-3	8.28	0.25	0.65	0.83	34.77
4-6	5.87	0.29	0.50	0.53	21.25
7-9	2.15	0.15	1.08	0.30	15.05
1-9	5.47	0.23	0.74	0.55	21.78
10-19	1.21	0.19	0.50	0.35	6.69
20-29	0.29	0.17	0.50	0.25	1.80
Total ..	2.13	0.19	0.58	0.38	11.77
No. of exposures	327	138	65	163	
No. at risk ..	511	2,437	511	2,437	

* Includes L series leukaemias, cancers, and controls.

† After standardizing for age-and-sex differences.

were 0.29 for M series leukaemias and 0.17 for other subjects. For peripheral x rays there were only chance differences between the exposure rates for the M series and other subjects.

Other prospective and retrospective surveys have shown that therapeutic doses of x rays applied to the spine increase the risk of developing leukaemias other than lymphatic leukaemias and that the risk is greatest between three and five years after exposure (Court Brown and Doll, 1957; Faber, 1958; Wise, 1961). In these earlier surveys there were relatively large numbers of acute cases among the irradiation leukaemias; in the present survey 9 of the 24 cases in the M series with trunk exposures were acute or subacute cases (38%), compared with 196 in the group as a whole (38%).

Diagnostic X Rays: Prevalence Rates and Exposure Rates

After exclusion of the 80 subjects with records of therapeutic x rays (see Table V), the survey population was reduced to 2,868 adults with the following specifications: M series (483); L series (496); cancers (933); and controls (956). In the combined group of cases and controls the overall prevalence rate for diagnostic x-ray exposures was 64%. This rate was higher for men (71%) than women (57%) (Table IX), higher for persons under 50 years (72%) than older persons (60%), and higher for controls (70%) than cases (62%). In the survey population as a whole, age and sex differences for diagnostic x-ray exposures were equally great for trunk and peripheral x-ray exposures, also for recent and remote examinations, but case/control differences were greater for peripheral x-ray exposures than for trunk x-ray exposures, and greater for x-ray exposures more than 10 years before the closing date (cases 23%, controls 36%) than for more recent x-ray exposures (cases 48%, controls 54%) (see also Table XI).

TABLE IX.—*Diagnostic X Rays. Prevalence Rates*

Cases and Controls	Diagnostic X-ray Exposures (All Sites). Years Before Closing Date		
	0-10	11+	All Years
	Prevalence Rates (%)		
Males	56.0	32.8	71.2
Females	43.6	29.0	57.0
Under 50 years	61.4	31.4	72.4
Over 50	45.1	24.5	60.1
Total No. of persons reporting diagnostic x rays	1,435	763	1,844

TABLE X.—*Diagnostic X Rays, Numbers of X Rays, and Numbers of Affected Persons in Four Diagnostic Groups*

	Years before Closing Dates	Leukaemias				Cancers (933)		Controls (956)		Total (2,868)	
		M Series (483)		L Series (496)							
		X Rays	Persons	X Rays	Persons	X Rays	Persons	X Rays	Persons	X Rays	Persons
		No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
Trunk x rays ..	0-5*	1,169	(165)	806	(170)	1,430	(319)	1,600	(360)	5,005	(1,014)
	6-10	430	(128)	458	(93)	745	(197)	1,085	(242)	2,718	(657)
	11+	771	(87)	816	(114)	856	(150)	1,291	(216)	3,734	(567)
	Total	2,370	(297)	2,080	(286)	3,031	(492)	3,976	(591)	11,457	(1,666)
Peripheral x rays	0-10	303	(61)	310	(66)	472	(103)	729	(152)	1,814	(382)
	11+	264	(50)	301	(46)	530	(103)	1,028	(166)	2,123	(365)
	Total	567	(107)	611	(103)	1,002	(197)	1,757	(302)	3,937	(709)
	All sites, all periods	2,937	320	2,691	300	4,033	559	5,733	665	15,394	1,844
*(0-5 years)	{ A B	34.2		34.3		34.2		37.7		35.4	
		7.08		4.74		4.48		4.44		4.94	
†(11+ years)	{ A B	10.4		9.3		11.0		17.4		12.7	
		5.28		6.54		5.2		6.2		5.82	

A = Prevalence rates. B = "Dose" rates. (See text.)

Unless we are prepared to make the absurd suggestion that diagnostic x rays protect against the subsequent development of malignant diseases (and that this protective action increases with passage of time!), these findings show that the healthy controls were better witnesses than the cases. It follows that any associations between diagnostic x rays and M series leukaemias which depend upon case/control comparisons are unlikely to exaggerate the true state of affairs, though they may understate it.

According to the scoring method which was used to assess numbers of exposures, the 1,844 men and women with records of diagnostic x rays included 1,666 who had 11,451 trunk exposures and 709 who had 3,937 peripheral exposures (see Table X). From the figures in Table X it is possible to calculate crude prevalence rates, exposure rates, and "dose" rates (that is, number of x-ray exposures per person examined). Figures in italics also show which of the subtotals were larger than one would expect if the x-ray exposures had been evenly distributed between the four diagnostic groups. Prevalence rates and dose rates corresponding to these exceptional numbers are also shown in Table X.

According to these crude rates both M series leukaemias and controls had more than their fair share of diagnostic x rays. The M series excess was due to the "usual" number of people reporting an exceptionally large number of trunk x-ray exposures during the five years immediately preceding the onset of symptoms; and the control excess was due to an exceptionally large number of people reporting the "usual" number of peripheral x-ray exposures more than 10 years before the closing dates.

Standardized prevalence rates (S.P.R.s) and standardized exposure rates (S.E.R.s) confirmed the findings based on crude rates, and showed that the M series excess for trunk x-ray exposures in the first quinquennium was accompanied by an exceptionally large number of subjects with at least 10 of these x-ray exposures (see Tables XI and XII).

To discover the reason for this concentration of diagnostic trunk x rays in the group which also had the highest incidence of trunk radiotherapy, the illness records were examined.

Comparison Between Illnesses and X-ray Exposures

During the first quinquennium more illnesses were reported by leukaemia patients than by cancer patients or controls (see Table XIII), but this was as far as the

resemblance between illnesses and x rays went (see Chart). The "extra" illnesses in the leukaemia groups were concentrated in the first year and affected the

TABLE XI.—*Diagnostic X Rays. Standardized Prevalence Ratios (Standard* 100)*

Sites Exposed	Years before Closing Dates	Standardized Prevalence Ratios				
		Leukaemias		Cancers	Controls	Totals (No. of Persons)
		M Series	L Series			
All sites	0-10	101	92	95	108	1,433
	Over 10	84	96	86	124	762
Trunk	0-10	104	97	96	104	1,313
	Over 10	89	117	82	114	567
Peripheral	0-10	91	104	83	119	382
	Over 10	84	70	87	136	365
At least 10 trunk x-ray exposures within 5 years of closing date		159	89	89	87	115
All sites, all periods		105	93	93	108	1,844

*Standard = Survey population as a whole.

TABLE XII.—*Standardized Exposure Ratios (Standard* 100), That is, Comparative Dose Rates in Four Main Groups*

Site	Years before Closing Dates	Standardized Exposure Ratios				
		Leukaemias		Cancers	Controls	No. of Exposures
		M Series	L Series			
Trunk	0-5	136	94	88	96	5,005
	6-10	93	98	84	120	2,718
Periphery	0-5	103	105	79	117	1,118
	6-10	93	92	81	126	696

*Standard = Survey population as a whole.

TABLE XIII.—*Comparison Between Annual Rates ($\times 100$) for Illnesses and X-ray Exposures During the First Decade*

Years before Closing Date	Case Groups			Controls	Totals
	M Series	L Series	Cancers		
Illnesses					
1	22.4	22.8	12.8	18.0	17.9
2	13.9	11.1	8.4	11.9	10.9
3	10.4	11.1	8.1	11.3	10.1
4	10.4	9.9	8.0	10.9	9.7
5	9.7	10.9	7.2	10.6	9.4
6	9.7	7.7	7.0	10.0	8.6
7	8.3	8.1	8.3	7.3	7.9
8	9.5	6.5	6.1	8.3	7.5
9	9.7	7.3	5.9	6.6	7.0
10	7.9	10.9	7.1	8.9	8.5
Mean 0-10	11.2	10.6	7.9	10.4	9.7
Trunk x rays					
1	39.5	38.9	35.3	37.6	37.4
2	47.8	34.1	28.9	37.1	35.7
3	56.5	28.8	30.7	36.9	36.8
4	49.9	27.2	23.5	27.5	29.9
5	48.2	33.7	35.0	28.2	34.7
6	23.6	22.2	19.8	21.0	21.3
7	22.8	23.2	18.9	23.0	22.1
8	18.2	13.7	12.5	23.7	17.4
9	9.9	15.9	17.3	23.4	17.9
10	14.5	17.3	11.4	22.3	16.6
Mean 0-10	33.1	25.3	23.3	28.1	26.9
Peripheral x rays					
1	11.4	7.6	4.1	11.7	8.5
2	4.8	11.1	8.2	8.3	8.1
3	7.0	8.3	3.8	10.0	7.2
4	13.7	8.3	6.8	9.7	9.2
5	3.3	4.8	4.9	5.9	5.0
6	3.9	11.1	3.1	7.2	6.0
7	7.0	5.6	6.9	7.9	7.0
8	2.7	0.8	3.8	4.0	3.1
9	5.4	2.4	1.3	6.7	3.4
10	3.5	2.2	3.6	6.8	4.4
Mean 0-10	6.3	6.3	4.6	7.6	6.2
Totals:					
Illnesses	540	526	735	992	2,793
Trunk x rays	1,599	1,264	2,175	2,685	7,723
Peripheral x rays	303	310	432	729	1,774
Nos. at risk	483	496	933	956	2,868

L series as much as the M series; extra trunk x-ray exposures in the leukaemia groups were spread over a four-year period (second to fifth) and affected the M series only. Extra illnesses in the leukaemia groups were confined to certain categories (see Table XIV; W.H.O., 1948) and were responsible for only a small proportion of the trunk x-ray exposures during the first quinquennium (see Table XV). For these illnesses, and for all other reasons listed in this Table, there was an excess of trunk x-ray exposures in the M series, and for each reason the number of exposures per person examined (dose rate) was higher in the M series than in the other groups.

Trunk X Rays During the First Decade

Throughout the first decade annual exposure rates for trunk x rays were higher for controls than for cases other than M series leukaemias, and both sexes contributed to these differences (see Table XVI).

TABLE XIV.—*Illnesses Reported During First Quinquennium*

Group	Illnesses: International Classification	Case Groups			Controls (%)	Total (%)
		M Series (%)	L Series (%)	Cancers (%)		
I	Infective	2.7	3.8	1.9	3.1	2.8
II	Tumours*	2.1	2.0	1.1	2.1	1.7
III	Endocrine and allergic	1.2	1.6	2.0	1.4	1.3
IV	Blood*	1.0	1.0	0.9	0.5	0.8
VI	C.N.S.	2.5	4.0	3.1	5.5	4.0
VII	Cardiovascular	4.1	4.0	3.0	6.6	4.6
VIII	Respiratory*	15.5	14.9	9.2	9.8	11.5
IX	Digestion	7.9	8.1	6.3	8.0	7.4
X	Genito-urinary*	7.4	5.4	2.9	4.4	4.6
XII	Skin	4.8	3.0	2.9	3.5	3.4
XIII	Musculo-skeletal	5.0	7.1	5.4	6.9	6.1
XVIII	Fractures*	5.2	3.8	3.2	4.5	4.1
	Other injuries	7.2	6.9	3.7	6.3	5.7
Total		66.6	65.7	44.5	62.7	58.0
No. of illnesses		322	326	415	599	1,662
Nos. at risk		483	496	933	956	2,868

* Designated "A" illnesses in Table XV.

First decade illnesses and diagnostic x rays (trunk). Continuous line = annual exposure rates for diagnostic trunk x rays. Broken line = ditto for illnesses. ○ = M series leukaemias. ● = Standard group (i.e., all other subjects).

During the second quinquennium exposure rates for M series leukaemias and all other cases were alike, but during a period which ran from the second to the fifth year male and female rates in the M series exceeded control rates.

In Table XII standardized exposure rates were based on the survey population as a whole. In Table XVII the standard group consists of L series leukaemias, cancers, and controls, and is compared direct with acute and chronic cases in the M series. In these subgroups there was a small deficit of trunk x-ray exposures during the second quinquennium and a much greater excess during the first quinquennium (45% in each group). For all cases in the M series, annual standardized exposure rates were significantly higher than standard between the second and the fifth years, and reached a maximum value of 185 in the fourth year.

Estimates of Risk

The way in which therapeutic and diagnostic x rays were distributed would be difficult to explain unless both (or neither) increased the risk of developing leukaemias other than lymphatic leukaemias. In view of what is already known about therapeutic x rays, it is reasonable to interpret these findings as evidence that certain types of leukaemia in adults can be induced by relatively small doses of x rays. The following estimates of risk are based on this assumption, and depend upon comparisons between M series leukaemias and other subjects in the survey population (standard group).

In order to make these estimates we defined an *x-rayed subject* as someone who had been exposed to potentially dangerous x rays (see below) before the closing date, and made three assumptions: (1) All *x-ray-induced* leukaemias were included in the M series (that is, none in the L series). (2) For M series leukaemias *not* induced by x rays, the ratio of *x-rayed subjects* to other subjects was the same as in the standard group (that is, this ratio can be used to estimate expected numbers in the M series leukaemias). (3) "Potentially dangerous x rays" were confined to trunk radiotherapy and diagnostic trunk x-ray exposure during the first decade.

In the standard group there were 29 subjects who had trunk radiotherapy, 1,085 who had diagnostic trunk x rays in the first decade, and 1,323 who had neither type of exposure. For M series leukaemias the corresponding numbers were 24 (radiotherapy), 243 (diagnostic x-ray exposures), and 244 (neither).

Hence the ratio of *x-rayed subjects* to other subjects in the standard group was:

$$29 \div 1,323, \text{ or } 0.022 \text{ for therapeutic x rays} \\ 1,085 \div 1,323, \text{ or } 0.820 \text{ for diagnostic x rays}$$

This gives as our estimate of expected numbers of M series leukaemias:

$$\begin{array}{l} \text{Not x-rayed (as defined)} = 244 \\ \text{Radiotherapy } (0.022 \times 244) = 5.37 \\ \text{Diagnostic x rays } (0.82 \times 244) = 200.08 \end{array} \left. \begin{array}{l} \\ \\ \end{array} \right\} \begin{array}{l} \text{Total expected} \\ = 449.45 \\ \text{(actual No. = 511)} \end{array}$$

Corresponding estimates for x-ray-induced cases in the M series were obtained by subtracting expected numbers from observed numbers—namely:

$$(24 - 5.37) + (243 - 200.08) = 18.63 + 42.92 = 61.55$$

(Radio-therapy) (Diagnostic x rays) (All exposures)

The final accounting of all cases in the M series group is shown in Table XVIII.

Osborn (1956) estimated that about 50 million x-ray examinations were performed by N.H.S. hospitals during the years 1951–5, two-thirds of which involved exposure of the chest or abdomen. During a five-year period which began and ended three years later (that is, 1954–8) there were 8,921 deaths due to leukaemias other than lymphatic leukaemias. If 8%, or 714, of these deaths were the result of diagnostic x-ray examinations during the earlier period, we arrived at an estimate of one leukaemia death for every 46,000 x-ray examinations of the chest or abdomen during 1951–5. The previous estimate for prenatal x-rays and malignant diseases in

TABLE XVI.—Annual Exposure Rates ($\times 100$) for Trunk X Rays

Years before Closing Dates	Annual Exposure Rates					
	Males			Females		
	M Series	Other Malignancies	Controls	M Series	Other Malignancies	Controls
1	46.7	51.3	51.1	34.1	19.0	23.3
2	62.9	41.4	48.3	36.3	17.9	25.5
3	70.5	35.4	46.0	45.8	23.7	27.4
4	60.0	34.4	30.3	42.7	13.3	24.6
5	58.1	36.6	35.0	40.7	32.0	21.2
6	36.7	23.5	25.2	13.6	17.3	16.7
7	17.1	24.5	30.1	27.1	15.4	15.6
8	23.3	16.0	33.5	14.3	9.3	13.5
9	8.6	20.8	40.1	11.0	12.1	6.0
10	10.0	16.5	34.4	18.0	9.8	9.6
Average rates:						
0–5	59.6	39.8	42.1	39.8	21.2	24.4
6–10	19.1	20.3	32.6	16.8	12.8	12.3
11–20	12.0	8.2	8.9	4.8	4.1	6.3
0–20	25.7	19.1	23.1	16.5	10.5	12.3
Nos. at risk	210	775	489	273	654	467
No. of exposures	1,078	2,964	2,262	902	1,376	1,151

TABLE XV.—Reasons for Diagnostic X Rays. Exposure Rates per Person Examined (First Quinquennium). Also Numbers of X-ray Exposures per Person Examined

Reasons for X Rays	Exposure Rate per 100 Persons at Risk					No. of Exposures per Person Examined					Total No. of Exposures
	Leukaemias		Cancers	Controls	M-O*	Leukaemias		Cancers	Controls	M-O*	
	M Series	L Series				M Series	L Series				
Digestive diseases ..	69.8	59.7	53.4	63.6	+14.0	9.9	9.0	8.0	7.6	+1.9	1,740
Respiratory ..	51.9	24.4	28.7	19.0	+28.0	5.3	3.7	3.6	2.3	+2.2	822
Genito-urinary ..	18.0	8.5	8.9	9.6	+8.9	7.9	6.0	7.5	7.7	+0.7	304
Injuries ..	10.7	7.5	5.8	5.3	+4.7	4.3	3.1	2.6	3.0	+1.5	194
Other ..	27.5	19.0	12.0	17.5	+11.9	4.0	4.1	2.9	2.9	+0.9	506
All illnesses ..	177.9	118.9	108.8	115.1	+64.5	6.3	5.5	4.9	4.5	+1.5	3,566
M.M.R., etc. ..	63.6	43.5	44.5	52.3	+16.2	2.2	1.8	1.8	1.9	+0.4	1,439
Total ..	241.5	162.5	153.2	167.4	+80.7	3.0	2.7	2.4	2.3	+0.6	5,005
"A" illnesses ..	50.4	27.0	28.7	20.4	+25.4	4.4	4.1	4.7	3.5	+0.3	851
Other reasons ..	191.1	135.5	124.5	147.0	+55.3	2.8	2.5	2.2	2.2	+0.6	4,154
Nos. at risk ..	483	496	933	956	—	—	—	—	—	—	—
No. of examinations ..	—	—	—	—	—	390	297	597	700	—	1,984

* Difference between M series leukaemias and all other subjects.

childhood was about one death per 1,000–2,000 examinations (Stewart *et al.*, 1958).

TABLE XVII.—*Diagnostic Trunk X Rays ($\times 100$). Annual Exposure Rates. Acute and Chronic Cases in M Series*

Years before Closing Date	Standard Group*	Annual Exposure Rates for Trunk X Rays (× 100)			Standardized Exposure Rates M Series (All Cases)
		M Series (Standardized Rates)		M Series. All Cases	
		Acute and Subacute	Chronic and Unspecified		
1	36.9	35.0	39.9	38.0	103
2	33.3	38.2	50.8	46.0	138
3	32.8	76.3	40.8	54.3	166
4	25.9	40.8	52.4	48.0	185
5	32.0	41.8	49.2	46.4	145
6	20.8	20.9	23.8	22.7	109
7	21.4	27.2	18.6	21.9	102
8	17.3	16.2	18.3	17.5	101
9	19.5	8.9	10.0	9.6	50
10	17.0	9.4	16.7	13.9	82
1st quinquennium	32.2	46.4	46.6	46.5	145
2nd quinquennium	19.2	16.5	17.4	17.1	90
2nd decade	6.8	8.2	7.5	7.8	112
All years (0-20)	16.3	19.8	19.8	19.8	122
Nos. at risk	2,385	185	298	483	483

* Standard group = L series leukaemias, cancers, and controls.

TABLE XVIII

	M Series Leukaemias		
	No.	%	Of X-rayed Subjects %
X-ray-induced cases:			
Radiotherapy ..	18.63	3.65	77.5
Diagnostic x rays ..	42.92	8.40	17.0
Other cases ..	449.45	87.95	—
Total ..	511	100	22.4

Estimates of Latent Intervals for X-ray-induced Leukaemias

Estimates of latent intervals for the 41.28 cases of leukaemia which were presumed to be caused by diagnostic x rays were based on the survey findings for trunk exposures during the eight years immediately preceding the closing dates (first eight intervals, see Table XIX).

TABLE XIX.—*Time Distribution of X-ray-induced Leukaemias in the M Series*

Years to Closing Date	M Series Leukaemias Induced by Diagnostic X Rays*	
	No.	%
1st	0.56	0.11
2nd	7.05	1.38
3rd	12.01	2.35
4th	12.26	2.40
5th	7.97	1.56
6th	1.02	0.20
7th	0.26	0.05
8th	0.15	0.03
9th and 10th	Nil	Nil
Total ..	41.28†	8.08†

*S.e. text.

†See footnote to Appendix.

It was already clear from the survey data that the percentage of leukaemias induced by diagnostic x rays (M_x cases) was a measure of the x-ray "dose" which was capable of initiating a leukaemic process. In other words, the larger the ratio of M_x cases to M_0 cases (that is, cases not induced by x rays) in the M series, the smaller the average number of trunk exposures for M_x cases.

This idea was a necessary part of the calculations (see below), which rested on three assumptions. First,

that the standardized exposure rates for trunk x rays during the stated intervals (first to eighth) was the same for M_0 cases and the standard group (see Table XVII). Secondly, that the "initiating dose" was the same in each of the eight years under consideration. Thirdly, that exposures made more than eight years before the closing dates had no effect.

On the basis of these assumptions, the average number of trunk x-ray exposures for M_x cases was found to be 8.55, and events which initiated leukaemic processes were distributed in time as shown in Table XIX. According to these figures, the commonest latent interval was between 36 and 40 months. If, however, we allow for the fact that more x-ray exposures were reported in the first three intervals than in more remote periods (memory bias), the interval with the largest number of cases would probably be nearer four years than three.

APPENDIX

ON ESTIMATING THE NUMBERS OF LEUKAEMIAS INDUCED IN THE DIFFERENT TIME INTERVALS AND THE MEAN NUMBER OF EXPOSURES FOR LEUKAEMIAS INDUCED BY DIAGNOSTIC X RAYS

BY

M. E. WISE

For these calculations* we ignore all subjects with trunk radiotherapy and place in one group all M series leukaemias *not* induced by x rays, whether x-rayed or not (M_0 in number=451.1). The remainder (M_x in number=41.3) are divided into eight interval groups (first to eighth before closing date). For any one of these intervals (say the t th) there are—in addition to the M_0 cases not induced by x rays— M_{xt} cases induced by x rays. The mean number of exposures (E_t) is known from Table XVII, and the total number of exposures is:

$$(M_0 + M_{xt})E_t.$$

This number depends on two averages: X_t exposures per x-ray-induced case; and W_t exposures per other case, and therefore equals:

$$M_{xt}X_t + M_0W_t$$

Thus for each time interval (t) we have

$$M_{xt}(X_t - E_t) = M_0(E_t - W_t) \quad (1)$$

We also have

$$M_{x1} + M_{x2} + \dots + M_{x8} = M_x \quad (2)$$

We now assume that the X_t 's are all the same, apart from random variations. (This means, in effect, that the distribution of possible intervals was independent of the number of x-ray exposures in any one year.) Putting all X_t 's = $\bar{X}$, we can determine $\bar{X}$ exactly. This is best achieved by writing, for all eight equations:

$$\frac{M_{xt}}{M_0} = \frac{E_t - W_t}{\bar{X} - E_t} = \frac{E_t - W_t}{\bar{X}} \left\{ 1 + \frac{E_t}{\bar{X}} + \frac{F_t^2}{\bar{X}^2} + \dots \right\}$$

and adding them. Thus:

$$\frac{1}{\bar{X}} \sum_t (E_t - W_t) = \frac{M_x}{M_0} = \frac{\sum_t \{E_t(E_t - W_t)\}}{\bar{X}^2} - \frac{\sum_t \{E_t^2(E_t - W_t)\}}{\bar{X}^3} \quad (3)$$

Where:

t = any one of the eight time intervals between induction of leukaemia by x rays and onset of symptoms (measured as differences between calendar years).

M_x = estimated number of M series leukaemias induced by x rays (41.3).

M_0 = estimated number of M series leukaemias not induced by x rays (451.1).

*These calculations were based on the assumption that 241 M series leukaemias had diagnostic trunk x rays in the first decade. This number should have been 243. Hence the small discrepancy between the values of M_0 given in the Appendix (41.3) and in the main text (42.9).

M_{xt} = estimated number of M series leukaemias induced by x rays t years before onset of symptoms.

E_t = standardized No. trunk x-ray exposures for M series t years before onset.

W_t = observed No. trunk x-ray exposures for standard group t years before onset.

Means (see
Table
XVII)

$\bar{X}$ = estimated number of trunk x-ray exposures per x-ray-induced case of leukaemia (that is, x rays per person).

Σ = sum of relevant quantities for all eight intervals ("sum over t").

With these values, the unknown $\bar{X}$ was found, by successive approximation, to be 8.55. The percentages of x-ray-induced leukaemias in the eight intervals were obtained by substituting this value for X_t in equation (1), with the results shown in Table XIX.

Discussion

The principal finding of the childhood survey, and the immediate reason for the present investigation, was a high incidence of prenatal x-ray exposures among the cases, particularly among the children who died from leukaemia or cancer between the ages of 5 and 8 years. There were no comparable differences between cases and controls in respect of other x-ray exposures or other events in the lives of the mothers and children, and we finally concluded that about 6% of childhood malignancies were due to irradiation *in utero*, and that these irradiation cases were concentrated in the 5-8 year age-group.

So unexpected was the suggestion that small doses of x-rays were capable of causing malignant diseases other than leukaemia that there was general reluctance to accept the evidence, which persisted even when essentially the same results were obtained by applying the same method to a group of children in Louisiana (Ford, Paterson, and Trueting, 1959). Critics were inclined to ascribe both results to the "wide network" method and to the vagaries of retrospective data. There were no precedents for the techniques employed, and, it was argued, the case/control differences might be artifacts caused either by faults in recording (observer error) or by faults in reporting (memory bias).

The doubts which were expressed about the reliability of the data were apparently confirmed when a prospective survey—that is, a follow-up of children irradiated *in utero*—produced negative results (Court Brown, Doll, and Hill, 1960). However, it subsequently transpired that these investigators had made two mistakes. They used a technique which excluded the possibility of discovering how many deaths had occurred from malignant diseases other than leukaemia, and they based their conclusions on a population with a mean age of less than 7 years. They also ignored the fact that the "normal" leukaemia death rate for the group as a whole concealed an excess of leukaemia deaths among the children who were over 7 years of age at the time of the follow-up and a deficit of deaths among the younger children (Stewart, 1961).

The unsatisfactory nature of the conclusions drawn from this survey were revealed when MacMahon (1962) published the results of a larger and more comprehensive prospective survey. These revealed a 50% excess of cancer and leukaemia deaths in the case groups as a whole (7,242 single births with records of abdominal or pelvic x-ray exposure during the relevant pregnancy), and 100% excess among the children who were between

the ages of 5 and 8 years at the time of the follow-up. During this inquiry MacMahon and Newill (1962) were also able to confirm two other findings of the original survey—namely, an excess of leukaemia deaths among first-born children and children with old mothers.

These findings have vindicated the method which was first used in the childhood survey and was later adapted to suit the needs of the adult survey. But they are not the only reason why the observed association between diagnostic trunk x-rays and M series leukaemias in the adult survey is unlikely to be an artifact. In the childhood survey the weakness of the results lay in the fact that they depended upon case/control contrasts; though it was unlikely (in view of the negative findings in respect of other x-ray exposures), the possibility that the mothers of dead children were, as a group, more reliable witnesses than the mothers of live children could not be excluded. In the adult survey essentially the same results would have been obtained if the records of healthy controls had been ignored and the M series leukaemias had been compared either with lymphatic leukaemias or with other malignant diseases.

The truly remarkable feature regarding the two investigations is that they have, between them, succeeded in identifying x-ray effects the existence of which was not even suspected. For whole body exposure of the foetus to diagnostic x rays the odds against initiating malignant disease were judged to be of the order of 1,000 to 1. For adults exposed to trunk x rays the odds must be more favourable. Yet even this small risk has been identified by means of retrospective data which are reputed to be both insensitive and unreliable. These data have also given a clearer demonstration of the latent interval for irradiation leukaemias than the one obtained from prospective data relating to x-ray treatments (Wise, 1961).

The present investigation has also shown that a simplified version of the original method of studying adult leukaemias will suffice in future. There is no doubt that, from a technical point of view, the most difficult part of the survey was the tracing of healthy controls. In future it will only be necessary to obtain records from a sufficiently large series of leukaemias (with or without other cancers) in order to test the validity of the results obtained so far. Instead of employing a team of survey doctors to collect the necessary data, this could be done by doctors in charge of cases, provided they were willing to use standard schedules and follow certain rules and conventions.

Summary

A survey is described which was designed to discover possible associations between diagnostic x rays and adult leukaemias, and was modelled on a recent survey of childhood leukaemias.

The data were obtained direct from 963 leukaemias, 60 lymphosarcomas, 951 other cancers, and 974 controls; cases and controls were seen in sets of three (leukaemia, cancer, control), and each member of a trio was matched for age, sex, district, and interviewer.

The cases were notified by hospital consultants in different parts of Britain and interviewed by medical officers of health on a regional basis. The controls were obtained from short lists of National Health Service patients which were compiled by clerks to local executive councils.

The leukaemias included 512 lymphatic leukaemias and 511 other leukaemias (so-called M series).

X-ray exposures which only involved the extremities (head and limbs) were reported more often by controls than cases, the control excess being confined to diagnostic radiographs which were taken more than 10 years before the closing dates (onset of symptoms or equivalent date for controls).

X-ray exposures which involved the trunk (chest and abdomen) were reported more often by M series leukaemias than other subjects, the excess for diagnostic x rays being confined to exposures which took place within eight years of the closing dates.

The difference between M series leukaemias and other subjects in respect of trunk x-ray exposures was greater for therapeutic than diagnostic exposures. For the latter type of exposure there was a peak incidence for M series leukaemias three to five years before the onset of symptoms (with no corresponding increase in the incidence of illnesses).

It was finally concluded that about 8% of leukaemias other than lymphatic leukaemias were caused by diagnostic x rays, and a further 3.6% by therapeutic x rays.

The survey was financed by grants from the Nuffield Provincial Hospitals Trust, the U.S.A. Public Health Service (Grant No. C-5392), the Medical Research Council, and the Nan Williams and Lena Grant Memorial Trust. The hospitals, public health departments, local executive councils, and survey doctors who co-operated are too many to mention by name, but we are indebted to them all, and would particularly like to thank the survey doctors for their great patience in tracing controls and interviewing them in their homes at awkward times of the day.

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"The design of an indicator is often—indeed usually—thought to be the business of the engineer, perhaps aided by someone—an artist or a 'stylist'—who adds an aesthetic touch, a twiddly bit, a strip of chromium, a dash of paint, or better still several dashes in clashing colours, of which a bilious yellow will be one. But in this problem of indicator design, machine and man meet in a relationship, for example, in the aircraft cockpit which must be regarded by engineer and human biologist together. Anatomy, physiology and psychology all come in to form what is sometimes known as human engineering, which means humanizing the machine, but not mechanizing the human. This attitude was present in embryo before the last war, during which it received considerable support from the armed Forces, and to-day they still possess permanent committee machinery for bringing together the engineering and biological points of view. Unfortunately, industry in general has been slower to grasp the importance of this relationship." (Bulletin of the North of England Industrial Health Advisory Service, March, 1962.)

MANAGEMENT OF ACUTE GASTRO-INTESTINAL BLEEDING MEASURING FAECAL BLOOD LOSS WITH ^{51}Cr

BY

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The validity of measuring faecal blood loss quantitatively by means of radioactive chromium is now generally accepted, and the method has been used in cases of chronic gastro-intestinal bleeding; the use of this method in acute gastro-intestinal bleeding has not been as extensively reported.

The premises which must be accepted are, firstly, that the greater part of the radioactivity in the gut must be excreted and not reabsorbed. This has been amply proved by Owen, Bollman, and Grindlay (1954), Roche, Perez-Gimenez, Layrisse, and di Prisco (1957), Ebaugh, Clemens, Rodnan, and Peterson (1958), and was confirmed when in two instances we introduced labelled red cells direct into the stomach and recovered all the activity in the faeces. Secondly, it must be assumed that only a small amount of ^{51}Cr which has been injected intravenously is found in the gut of normal subjects; published findings range up to the equivalent of about 1.3 ml. of whole blood excreted in the faeces per day (Roche *et al.*, 1957; Ebaugh *et al.*, 1958; Hughes Jones, 1958; Levin, Hart, and Bothwell, 1959; Cameron, 1960). As will be shown, this is generally less than the lowest activity measurable with our apparatus.

Most studies have been carried out on patients in whom chronic gastro-intestinal blood loss has been suspected, such as cases of hookworm disease (Roche *et al.* 1957), various other indolent gastro-intestinal lesions (Bannerman, 1957; Ebaugh *et al.*, 1958; Owen *et al.*, 1954; Hughes Jones, 1958; Levin *et al.*, 1959), and with ingestion of salicylates, steroids, and phenylbutazone (Scott, Porter, Lewis, and Dixon, 1961). From these papers there seems little doubt that the quantitative measurement of blood loss in the stools by the radiochromium method may be of value in managing and diagnosing cases of chronic anaemia.

Bannerman (1957) in a small series of cases suggested that the site of bleeding might be estimated by this method; Ebaugh *et al.* (1958) claim to have sited the bleeding by intubation in eight out of nine cases, and Levin *et al.* (1959) suggest that the use of gut markers may help in siting the bleeding-point.

Tudhope (1958) carried out a careful analysis of 30 patients with acute gastro-intestinal bleeding, using ^{51}Cr ; he placed emphasis on red-cell survival and volume measurements, but in some cases he measured faecal blood loss as well.

It is the purpose of this paper to evaluate the use of measuring faecal blood loss by means of radioactive chromium in the management and assessment of cases of acute gastro-intestinal bleeding. This work was carried out in a busy acute medical unit where prolonged studies were not practicable. Our object was to compare