forced to stand to obtain relief from pain. Sedatives were given as required, and pethidine was sometimes administered in the early stages when pain was severe.

Contributory factors, such as diabetes mellitus, hypertension, and obesity, were corrected so far as was possible. Cases with serious hypertension, however, were not included in the series analysed.

The only coronary vasodilators that were used in this study were trinitrin, p.r.n., and pentaerythritol tetranitrate, in the form either of "peritrate" (10 mg.) or of "myocardol" (30 mg.), in doses of one or two tablets three times a day, one hour before meals.

Adverse blood lipid patterns that did not respond to diet alone were countered with 40–50 oz. of corn oil daily or with nicotinic acid, the dose of which was gradually increased from 100 mg. t.d.s. to 500 t.d.s., if well tolerated. Such treatment was rarely given unless the serum cholesterol remained obstinately high, between 350 and 700 mg./100 ml., and was uninfluenced by the decision to give anticoagulants or not. Neither triparanol ("MER-29") nor oestrogens were used in this series.

During 1958 iproniazid ("marsilid") proved helpful in relieving intractable cardiac pain in states of coronary insufficiency, but did not influence the fundamental course of the disease (Towers and Wood, 1958). The hypotensive, anabolic, hepatotoxic, and neuromuscular side-effects of iproniazid, however, limited its use. During the last two years other mono-amine oxidase inhibitors relatively free from these side-effects have been tried, particularly isocarboxazid ("marplan"), but on the whole they have been less effective. It is repeated for emphasis that these substances do not alter the fundamental course of the disease. They are best used temporarily, to overcome undue suffering when the patient is incapacitated, and should usually be withheld before he returns to work, for masking angina pectoris may be dangerous.

Summary

The clinical features and natural course of acute coronary insufficiency are described.

The results of anticoagulant therapy in 100 cases are compared with those of conservative management in 50 cases.

Cardiac infarction developed within two months in 3% of the treated cases and in 22% of the controls.

The mortality of treated cases was one fifth that of the controls.

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A new edition of *Introductory Manual on the Control of Health Hazards from Radioactive Materials* has now been published in the Medical Research Council's regular series of Memoranda. As the preface to the volume indicates, it is essentially an introductory manual intended mainly for the guidance of those concerned with the manipulation of radioactive materials in laboratories and elsewhere. Publications dealing in greater detail with various aspects of hazards from radiation are mentioned in the text and in the bibliography. (H.M.S.O., M.R.C. Memorandum No. 39, price 1s. 9d. net.)

MORTALITY FROM PRIMARY TUMOURS OF BONE IN ENGLAND AND WALES

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The suggestion that small doses of radiation might be capable of inducing cancer has stimulated interest in the incidence of some of the rarer forms of the disease. In particular, it has been suggested that the very small amounts of radium and other radioactive substances which are located in the skeleton might be responsible for some cases of bone tumour, and that the incidence of such tumours might vary from one geographical area to another, depending upon the radioactivity of local food and water supplies (Marinelli, 1958). Experiments have shown that large doses of radioactive substances will regularly cause bone tumours in a high proportion of animals (Brues, Lisco, and Finkel, 1946; Finkel, 1956), and observations on patients given deep x-ray therapy (Vaughan, 1956), and on persons exposed to radium therapeutically or in the course of their work (Martland, 1931; Aub, Evans, Hempelmann, and Martland, 1952; Looney, Hasterlik, Brues, and Skirmont, 1955; Looney, 1956) have demonstrated that ionizing radiations can also cause bone tumours in man. It does not follow, however, that a similar effect will be produced by smaller doses, and it is possible that very small doses will not produce any risk of cancer at all.

The maximum effect of small doses can be estimated by assuming (1) that the effect is proportional to the dose, and (2) that the total natural incidence of cancer is attributable to natural background radioactivity. This method was used by the United Nations Scientific Committee on the Effects of Atomic Radiation (1958) to estimate the maximum amount of bone cancer which might be due to the ingestion of very small quantities of strontium-90 and of other radioactive substances; but they thought it reasonable to assume that not more than 10% of primary bone tumours could be attributable to natural radioactivity. They assumed that the annual incidence of primary bone tumours was between 5 and 10 cases per million persons per year, and they therefore made their calculations on the basis that "a natural radiation level of 9 rem per 70-year human lifetime" would give rise to between 5 and 10 cases per million persons in a 10-year period.

One of the many difficulties in making this type of calculation is that there is no accurate measure of the incidence of bone tumours. The disease is rare and data collected from cancer registries relate to too short a

*Since the completion of the work Dr. Mackenzie has died.

period or to too small a population to provide a reliable estimate of incidence. Mortality data are available for larger populations; but, in this instance, the certified cause of death is thought to be often insufficiently accurate. For example, the death rate attributed to primary bone tumours in England and Wales fell between 1947 and 1957 from 28 per million men to 16 per million and from 17 per million women to 12 per million. There is no reason to suppose that the true incidence of the disease fell during this period, and it seems likely that the change in the recorded mortality was largely due to the more accurate diagnosis of other types of cancer presenting with metastases in bones.

The present study was therefore undertaken, at the request of the Medical Research Council's Committee on Protection Against Ionizing Radiations, to obtain a more reliable estimate of the mortality from bone tumours in this country. It was realized that mortality would, at best, give only an indirect estimate of incidence; but, in the absence of any dramatic change in the efficacy of treatment, it seemed reasonable to use mortality rates as an indication of a change in incidence with time or of a difference in incidence between different areas. Since it was proposed to obtain data for an entire population, it was hoped that the results would also provide reliable comparisons of the impact of the various types of tumour in men and in women at different ages.

Method

The General Register Office has extracted records of all deaths attributed to malignant tumours of the bone (No. 196 in the International Statistical Classification of Diseases, World Health Organization, 1949) which occurred in England and Wales in the three years 1951-3 among persons aged under 65 years. Persons aged 65 and over were excluded, as it was thought that the proportion in which the cause of death had been adequately investigated would be too small for the purpose of the present inquiry. Three years were studied, to provide enough data for analysis by sex and age and by the site of the affected bone, and these particular years were chosen because 1951 was the earliest year for which suitable records were still available and 1953 was the year in which the first megaton hydrogen bomb was exploded and the stratosphere was contaminated with appreciable amounts of fission products.

From the death entry, information was obtained about the sex and age of the patient, the place of death, the usual place of residence, and the occupation. The certified cause of death was also copied in full. If the case had been registered in the national cancer registration scheme and details of the basis of the diagnosis were available, the details were extracted from the records. If not, and the patient had died in hospital, the hospital was written to and inquiries were made about (1) the final hospital diagnosis; (2) whether the diagnosis had been made at necropsy or operation, or, if not, the nature of the evidence on which the diagnosis had been based; and (3), if a microscopical examination had been made, the nature of the histological report. If there was no evidence that the patient had attended hospital, the doctor who signed the death certificate was asked whether the diagnosis had been made after investigation in a hospital. If so, he was asked the name of the hospital and the approximate date of attendance; if not, he was asked to give the evidence on which the diagnosis was based.

The cases in which additional information was obtained were reviewed individually by us and were classified in three groups according to the certainty and nature of the diagnosis: (1) satisfactory evidence of a primary bone tumour; (2) satisfactory evidence that the condition was not due to a primary bone tumour; and (3) evidence of presence or absence of a primary bone tumour uncertain. Cases with histological evidence of the type of tumour were classified in seven groups—that is, osteosarcoma, chondrosarcoma, fibrosarcoma, giant-cell tumour, chordoma, Ewing's tumour (including angioendothelioma), and other or unspecified sarcoma.

In general, the hospital discharge diagnosis was accepted as the final diagnosis unless (1) it appeared to relate to an irrelevant admission and was clearly unrelated to the cause of death, or (2) there was additional and unequivocal evidence that another diagnosis was preferable—for example, necropsy evidence or a conclusive histological report which appeared not to have been taken into account. If the hospital diagnosis was itself uncertain—for example, ? sarcoma, ? secondary carcinoma of the ilium—or the hospital report provided conflicting evidence, the diagnosis was classified as uncertain. Diagnoses referring to sarcoma of a part of the body without specifying a bone—for example, sarcoma of thigh—were regarded as relating to soft-tissue tumours so long as the rest of the evidence was consistent with this diagnosis. A diagnosis of this type would, however, have led to the classification of the case as one of primary bone tumour if it was accompanied by histological, radiological, or surgical evidence that the tumour arose from bone. If the diagnosis implied that the primary tumour involved two contiguous bones, the first named was regarded as the site of origin.

Tumours were classified as being of a specific histological type only when there was definite histological evidence to this effect. A hospital diagnosis of "osteogenic sarcoma of femur" was not regarded as sufficient to justify classifying the tumour as of this particular histological type, unless a histological report which substantiated the diagnosis was also given; in the absence of such a report, the tumour was classified as a primary tumour of bone of unspecified histological type. Reticulum-cell sarcomas were classified as bone tumours only if there was positive evidence that the tumour was regarded as arising from bone. Myelomatosis was not regarded as a bone tumour; but myeloma (with or without reference to plasma cells) was, if it appeared to have been a solitary lesion. Adamantinomas of the jaw arise from the epithelial covering of the teeth and were not classified as bone tumours; the one adamantinoma of the tibia was regarded as a bone tumour, although the origin of this type of tumour is obscure.

When further information was obtained the data on the death certificate were not used in reaching the final diagnosis unless: (1) the hospital data clearly indicated a primary bone tumour but did not specify the bone of origin; or (2) Paget's disease was mentioned on the certificate but was not mentioned by the hospital. In these circumstances the information on the certificate was used to determine the bone of origin or to classify the case as one associated with Paget's disease.

When additional information was obtained the data were used to compare the certified diagnosis with the final diagnosis. This comparison enabled an estimate to be made of the reliability of the certified cause of death,

subdivided according to the place of death, age and sex of the patient, the affected bone, and the histological description of the tumour given by the certifying doctor. On this basis it was possible to estimate the number of cases of true primary bone tumour likely to have been included among the cases for which no further information had been obtained. An estimate of the total mortality from primary bone tumours could then be made by summing the cases for which the diagnosis was confirmed, and an estimated number of true bone-tumour cases corresponding to those in which the only information was that provided by the death certificates. The validity of this procedure is discussed below.

Results

Altogether, 1,180 deaths were attributed to primary tumours of the bone in persons under 65 years during the three years of the investigation (Registrar-General, 1953, 1954, 1955). Of these, 11 were excluded because the death related to a foreign national (five cases) or because the cause of death had obviously been wrongly assigned (six cases). Additional information was obtained for 990 of the remaining 1,169, leaving 179 (15.3%) in which the only information available was that given on the death certificate. Among the 990 cases in which further information was obtained there were 516 (52.1%) in which the correct diagnosis was thought to have been a primary bone tumour. In a further 25 cases (2.5%) the possibility that there was a primary bone tumour was not excluded and the diag-

nosis was regarded as uncertain. In the remainder (45.4%) no primary bone tumour was thought to have been present. Histological evidence of the nature of the tumour was available in 77% of the cases in which the diagnosis of a primary bone tumour was accepted. The distribution of the various histological types is shown in Table I.

TABLE I.—Number of Tumours of Each Histological Type Accepted as Primary Tumours of Bone

Type of Tumour	No. of Cases
Osteosarcoma	144
Chondrosarcoma	66
Spindle-cell sarcoma	27
Fibrosarcoma	24
Ewing's tumour of bone	19
Giant-cell tumour	13
Reticulosarcoma	13
Chordoma	12
Round-cell sarcoma	8
Various (myeloma 2, angiosarcoma 2, myxosarcoma 2, adamantinoma 1, leiomyosarcoma 1, liposarcoma 1, myxochondrosarcoma 1, myxofibrosarcoma 1)	11
Undifferentiated	14
Sarcoma, unspecified or "mixed cell"	44
Total with histological evidence	395
No histological evidence	121
Total accepted tumours	516

Accuracy of Diagnosis

The accuracy of the diagnosis was not the same in all the subgroups examined. Among the 443 patients who died in hospital the diagnosis was confirmed in 253 (57%), whereas it was confirmed in 263 (48%) of the 547 patients who died elsewhere. A similar difference

TABLE II.—Number and Percentage of Cases in which the Certified Diagnosis of a Primary Bone Tumour was Confirmed, Divided by Sex and Age

Sex	Final Diagnosis	Age in Years														All Ages
		0—	5—	10—	15—	20—	25—	30—	35—	40—	45—	50—	55—	60—64		
Male	Primary bone tumour	4		25	53	28	20	13	11	17	21	35	37	47	318	
	Other diagnosis*	5	7	4	9	7	8	8	15	20	27	40	54	60	262	
	Per cent. primary bone tumour	44%	78%		84%		73%		44%		46%		42%		55%	
Female	Primary bone tumour	2	10	14	28	23	9	13	10	13	12	20	15	29	198	
	Other diagnosis*	4	3	5	4	5	10	9	7	11	20	34	44	56	212	
	Per cent. primary bone tumour	33%	75%		84%		55%		56%		37%		31%		48%	
Male and female	All diagnoses	15	25	48	94	63	47	43	43	61	80	129	150	192	990	
	Per cent. primary bone tumour	40%	68%	81%	86%	81%	62%	60%	49%	49%	41%	43%	35%	40%	52%	

* Cases in which it was uncertain whether a primary bone tumour was present are included here under "other diagnosis"; they are listed in the Appendix.

TABLE III.—Number and Percentage of Cases in which the Certified Diagnosis of a Primary Bone Tumour was Confirmed, Divided by the Bone of Origin and the Pathological Description of the Tumour

Certified Bones of Origin	Reference to Paget's Disease on Death Certificate:		No Reference to Paget's Disease on Death Certificate									All Cases Certified as Malignant Bone Tumour		
			Certified Specific Histological Type of Sarcoma:		Certified as Sarcoma Unspecified:		Certified as Carcinoma, Cancer, etc.:							
	No. with Final Diagnosis		Per cent. Primary Bone Tumour	No. with Final Diagnosis		Per cent. Primary Bone Tumour	No. with Final Diagnosis		Per cent. Primary Bone Tumour	All Diagnoses	Per cent. Primary Bone Tumour			
	Primary Bone Tumour	Other Diagnosis		Primary Bone Tumour	Other Diagnosis*		Primary Bone Tumour	Other Diagnosis*						
Upper limb	2	0	100%	14	1	93%	28	14	67%	0	5	0%	64	69%
Lower	21	0	100%	81	11	88%	134	50	73%	5	9	36%	311	77%
Jaw (upper and lower)	1	0	100%	6	3	67%	16	22	42%	2	96	2%	146	17%
Ethmoid	0	0	—	0	0	—	0	3	0%	0	29	0%	32	0%
Rest of skull	2	0	100%	4	3	57%	6	8	43%	0	18	0%	41	29%
Vertebrae or spine unspecified	1	0	100%	12	2	86%	4	17	19%	2	70	3%	108	18%
Sacrum	0	0	—	15	1	88%	7	8	47%	2	8	20%	41	59%
Shoulder girdle†	0	0	—	4	1	80%	12	12	50%	1	2	33%	32	53%
Ribs or sternum	0	0	—	16	1	94%	16	11	59%	0	13	0%	57	56%
Pelvis‡	6	0	100%	30	7	81%	29	21	58%	1	11	8%	105	63%
Multiple or unspecified	11	1	83%	23	3	88%	2	4	33%	0	9	0%	53	68%
All bones	44	1	98%	205	33	86%	254	170	60%	13	270	4%	990	52%

* See footnote to Table II. † Including shoulder unspecified. ‡ Including hip unspecified.

was recorded between men (55% confirmed tumours) and women (48% confirmed). Other factors, however, were found to affect the reliability of the diagnosis to a greater extent. Table II shows an analysis of the results according to the sex and age of the patient, and it is seen that the reliability varied from 86% at ages 15-19 years to about 40% at ages 45 to 64 years. Still greater differences were recorded when the data were analysed according to the anatomical site of the tumour and the pathological description given by the doctor who signed the death certificate (Table III). The reliability varied from 77% when the primary was said to have arisen from bones of the lower limb to 0% when the origin was in the ethmoid, and from 98% when Paget's disease of bone was said to have been associated with the tumour to 4% when the presence of Paget's disease was not referred to and the growth was described as carcinoma or by some non-specific term such as cancer, malignant neoplasm, or malignant new growth.

In view of the large differences in the various anatomical and pathological groups, the possibility has to be considered that the smaller differences observed in the other groups may result from differences in the distribution of the place of death and the sex and age of the patient in the anatomical and pathological groups. A calculation has therefore been made of the significance of each of the five variables examined when the effect of the other four factors is taken into account. First the number of age and anatomical groups shown in Tables II and III was reduced by combining groups in which the proportions of confirmed diagnoses were similar. Tables were then prepared showing the proportion of confirmed diagnosis in 480 subgroups defined by place of death (hospital or elsewhere), sex, age (0-9 years, 10-24 years, 25-34 years, 35-44 years, and 45 years and over), anatomical site (limbs, jaws, ethmoid, rest of skull, spine excluding sacrum, and other and unspecified sites), and pathological description (Paget's disease present and, in the absence of Paget's disease, specified type of sarcoma, unspecified sarcoma and other descriptions). The expected number of confirmed cases could then be calculated separately for each characteristic independently of variation of the others.

For example, there were 31 cases described as sarcoma of a limb bone, without specification of the histological type and without reference to Paget's disease, in men aged between 10 and 24 years who died at home; and there were 20 similar cases in women. Altogether the diagnosis was confirmed in 47 cases, so that the expected numbers of confirmed cases in men and in women, if there was no difference in the reliability of the diagnosis in the two sexes, would be $31 \times 47/51$ (i.e., 28.57) and $20 \times 47/51$ (i.e., 18.43). The numbers actually observed were 29 and 18. Similar calculations were made for each of the other subgroups, and the final comparison was made by summing all the expected numbers separately for each sex and comparing the totals with the observed numbers of confirmed cases in men and in women.

The results are shown in Table IV. They show clearly that one factor is of much greater importance than all the others in determining the reliability of the certified diagnosis of a primary bone tumour—and that is the certifying doctor's pathological description of the disease.

Evidently the diagnoses are intrinsically more reliable than would appear on first examination of the crude mortality data. The responsibility for the low propor-

tion of cases in which the diagnosis of a primary bone tumour is confirmed lies not so much with the certifying doctor as with the international rules, which result in classifying "carcinoma of the jaw," "carcinoma of the ethmoid," and "cancer of the vertebra" as primary bone tumours. As might have been anticipated, the first two diagnoses are used to describe carcinomas of the

TABLE IV.—*Number of Confirmed Cases of Primary Bone Tumour Divided Separately by Place of Death, Sex and Age of Patient, Affected Bone, and Pathological Description on the Death Certificate, Compared with the Number Expected After Allowing for the Effect of the Other Four Characteristics*

Characteristic	No. of Cases Observed	No. of Cases Expected	Observed Cases as Percentage of Expected	χ^2	n	P
Place of death:						
Hospital	251	244.6	102.6	0.318	1	0.5 < P < 0.7
Elsewhere	265	271.4	97.6			
Sex:						
Male	318	311.7	102.0	0.322	1	0.5 < P < 0.7
Female	198	204.3	96.9			
Age:						
0-9 years	23	24.3	94.7	5.899	4	0.2 < P < 0.3
10-24	171	147.5	115.9			
25-34	55	57.6	95.5			
35-44	51	54.5	93.6			
45-64	216	232.1	93.1			
Bone:						
Limb bone	285	261.0	109.2	11.075	5	P = 0.05
Ethmoid	0	3.0	0.0			
Jaw	25	31.0	80.6			
Rest of skull ..	12	15.3	78.4			
Vertebrae excluding sacrum ..	18	28.7	62.8			
Other bones and multiple and unspecified sites ..	176	177.0	99.4	54.318	3	P < 0.001
Pathological description:						
Paget's disease present	44	27.6	159.4			
Paget's disease not referred to:						
Specified type of sarcoma	205	166.0	123.5			
Sarcoma unspecified	254	264.3	96.1			
Other descriptions	13	58.1	22.4			

mucous membrane covering the jaw bones and lining the ethmoid sinus, and the third corresponds to a diagnosis of bony metastases from a carcinoma elsewhere in the body. When there is evidence to show that the neoplasm actually originated in bone, the certifying doctor usually describes it as a bone sarcoma and he often adds its exact histological description.

In present circumstances, however, it would be unwise to ignore all the other factors completely. After the effect of the pathological description is taken into account there still appears to be some variation in the reliability of the diagnosis applied to different bones. No cases of primary tumour of the ethmoid were confirmed, even though a few were described as sarcomas, and the reliability of the diagnosis of sarcoma of the vertebra was less than that of sarcoma of the femur. There is no reason to suppose that there is any great variation between most of the bones; but, on the present evidence, it seems reasonable to distinguish five groups within which the diagnoses may be regarded as equally reliable. These are, in order of reliability of the diagnosis, (1) limb bones; (2) sacrum, pelvis, shoulder-girdle, ribs, and sternum; (3) skull, including jaw but excluding ethmoid; (4) spine, excluding sacrum; and (5) ethmoid. Cases in which the site of the bone is not stated or more than one bone is specified have been classed in group 2.

After allowance is made for anatomical site and pathological description there is little difference in the reliability of the diagnosis in different age-groups. The

differences are not statistically significant, but until more evidence is obtained it seems better to assume that there is some difference between age-group 10-24 years and the others. If these three factors are taken into account the differences between the reliability of the diagnosis in men and in women, and between patients who die in hospital and elsewhere, can be ignored.

Estimate of Mortality Rates

The 990 cases in which further information was obtained about the cause of death have therefore been classified in four pathological groups and subdivided in five bone and two age subgroups. The total numbers of cases in each subgroup and the numbers in which the diagnosis was confirmed are shown in Table V.

From these data it is possible to estimate the number of true primary bone tumours which corresponded to the 179 certified causes of death for which no further information was obtained. For example, a death attributed to "sarcoma of the pelvis" in a man aged 55 years may be estimated as having 54 chances in 103 of being due to a primary bone tumour, and the death can be regarded as contributing, on average, 0.52 (54/103) of a case in the particular sex and age group. The validity of this estimate depends partly on the number of cases for which information had been obtained and partly on the degree of similarity between those for which information was obtained and those for which it was not. A comparison between the two groups is shown in Table VI. It is understandable that it was more difficult to obtain information from a general practitioner than from a hospital and more deaths occurred outside hospital among the group without further information than among those with. This difference is presumably reflected in the higher proportion of deaths in the oldest age-group and in the greater proportion of deaths attributed to malignancy of the spine and in the greater proportion not specified as sarcoma. All these factors can, however, be taken into account by using the proportion appropriate to each case, which is shown in Table V. The proportions are, at best, only approximations; the accuracy of the diagnosis in the unknown group may have been affected by other factors that have not been taken into consideration—for example, the age of the certifying doctor and the place of residence—but in the absence of more accurate information it seems reasonable to use these proportions to provide the best available estimate. On this basis, the number of primary bone tumours corresponding to the group of 179 certified deaths without further information is 81.4. The reliability of the diagnosis in this group as a whole (45%) is, as would

be expected from inspection of Table VI, somewhat lower than the reliability in the main group for which further information was obtained (52%).

If the 81 presumed cases are added to the 516 confirmed cases of primary bone tumour, an estimate is obtained of the total mortality from primary bone tumours in England and Wales in 1951-3. Age-and-sex specific death-rates calculated in this way for 11 bones or groups of bones are shown in Tables VII and VIII. These rates are minimum rates, since 25 cases (listed in the Appendix) in which the diagnosis was uncertain have been regarded as not being primary bone tumours and no allowance has been made for the misdiagnosis of primary bone tumours under some other rubric.

An estimate of the maximum effect of the first factor can be made by assuming that in all 25 cases a primary bone tumour was, in fact, the cause of death. If this is done, the proportions shown in Table V are slightly altered and the estimated number of true bone tumours corresponding to the 179 cases in which no further information was obtained is increased to 47%. The effect on the estimates of the total mortality rates is small; the estimate of the annual male mortality rate at all ages under 65 years is increased from 62.9 to 65.3 per 10,000,000 men and of the female mortality rate from 38.9 to 41.6 per 10,000,000 women.

On present information it is impossible to make any quantitative estimate of the number of primary bone

TABLE VI.—Comparison Between Cases With and Without Information Additional to the Certified Cause of Death

Characteristics	Cases with Further Information		Cases without Further Information	
	No.	Per cent.	No.	Per cent.
Place of death:				
Hospital	443	45	29	16
Elsewhere	547	55	150	84
Sex:				
Male	580	59	96	54
Female	410	41	83	46
Age:				
0-9 years	40	4	6	3
10-24	205	21	24	13
25-44	194	20	35	20
45-64	551	56	114	64
Bone:				
Limb bone	375	38	64	36
Ethmoid	32	3	4	2
Rest of skull	187	19	32	18
Vertebrae, excluding sacrum	108	11	35	20
Other bones and multiple and unspecified sites	288	29	44	25
Pathological description:				
Paget's disease present	45	5	6	3
" not referred to:				
Specified type of sarcoma	238	24	33	18
Sarcoma unspecified	424	43	74	41
Other descriptions	283	29	66	37

TABLE V.—Number of Cases Certified as Bone Tumours and Number of Confirmed Cases, Divided by Pathological Description, Affected Bone, and Age of Patient

Paget's Disease	Histological Description of Tumour	Age of Patient (in Years)	Number of Deaths Attributed to Tumours of									
			Limb Bones		Other and Unspecified Bones		Skull, Excluding Ethmoid		Vertebrae, Excluding Sacrum		Ethmoid	
			Con- firmed	Total	Con- firmed	Total	Con- firmed	Total	Con- firmed	Total	Con- firmed	Total
Present	All descriptions	25-64	23	23	17	18	3	3	1	1	—	—
	Specified type of sarcoma	10-24 Other ages	48 47	53 54	23 65	26 75	2 8	2 14	1 11	1 13	—	—
Absent	Sarcoma unspecified	10-24 Other ages	74 88	81 145	12 54	19 103	5 17	6 46	3 1	7 14	— 0	— 3
	Other descriptions	10-24 Other ages	1 4	1 18	2 2	3 44	0 2	2 114	0 2	3 69	0 0	1 28

tumours which have not been diagnosed, or in which the cause of death has been certified in such a way that the death has been misclassified. Likely sources of error include the classification of a primary bone tumour as tumour of soft tissue, reticulosarcoma, metastatic neuroblastoma, or as giving rise to carcinomatosis of

unknown origin. It seems unlikely, however, that a large proportion of cases will have been misdiagnosed, as (1) the common types of osteogenic sarcoma and chondrosarcoma arise in an accessible site, and (2) young people who develop a fatal illness are nearly always investigated in hospital.

TABLE VII.—Male Mortality from Primary Tumours of the Bone in England and Wales, 1951-3

Site of Primary Tumour	Annual Death Rate per 10,000,000 Males Aged (in Years):													
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
Humerus	0.0	1.9	16.1	11.9	4.5	4.7	1.7	3.4	9.4	5.2				
Radius or ulna .. .	0.0	1.9	0.0	0.0	0.0	0.0	0.0	1.1	2.3	0.6				
Femur .. .	3.7	3.8	20.5	60.7	28.9	13.1	12.0	16.7	47.0	20.6				
Tibia or fibula .. .	0.0	0.0	18.4	43.0	17.9	4.5	1.0	4.8	4.9	8.0				
Other limb bone .. .	0.0	0.0	0.0	7.2	0.0	1.0	1.7	1.1	2.6	1.4				
All limb bones .. .	3.7	7.6	54.9	122.7	51.4	33.0	13.7	9.5	22.8	20.9	34.4	52.1	82.8	35.7
Mandible or maxilla .. .	0.0	1.9	1.9	0.0	4.2	2.1	4.7	1.2	6.5	2.6				
Rest of skull .. .	0.0	0.0	0.0	2.4	0.0	1.0	0.0	1.2	5.5	1.1				
Spine (including sacrum) .. .	1.8	0.0	4.6	4.8	4.5	3.1	2.1	7.9	11.1	4.5				
Ribs .. .	0.0	1.9	0.0	2.4	6.8	2.1	4.0	7.2	18.9	5.0				
Clavicle or scapula .. .	0.0	1.0	0.0	0.0	4.5	2.1	1.0	7.8	9.7	3.2				
Pelvis .. .	1.8	1.9	2.3	5.0	2.3	3.1	4.2	17.0	39.2	9.1				
Bones, other than in limbs .. .	3.7	6.7	8.8	14.5	22.3	14.7	12.4	16.9	15.1	24.4	63.1	75.3	108.9	25.5
Bone, unspecified .. .	1.6	0.0	0.0	0.0	0.0	1.0	2.1	2.8	5.6	1.7				
All bones .. .	9.0	14.4	63.7	137.2	73.6	47.8	28.2	26.4	41.9	50.5	97.5	134.7	195.3	62.9

TABLE VIII.—Female Mortality from Primary Tumours of the Bone in England and Wales, 1951-3

Site of Primary Tumour	Annual Death Rate per 10,000,000 Females Aged (in Years):													
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
Humerus .. .	0.0	6.0	2.4	9.6	4.5	1.0	3.0	2.8	6.8	3.7				
Radius or ulna .. .	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3	0.2				
Femur .. .	1.9	10.0	14.1	42.4	13.6	7.7	9.2	15.2	26.4	14.6				
Tibia or fibula .. .	0.0	0.0	16.3	7.3	13.4	0.0	1.1	5.5	8.1	4.7				
Other limb bone .. .	0.0	0.0	0.0	0.0	0.0	1.0	1.0	0.0	1.3	0.5				
All limb bones .. .	1.9	16.0	32.8	59.3	31.6	8.9	10.7	12.3	16.1	13.5	34.2	30.9	58.2	23.6
Mandible or maxilla .. .	2.5	2.0	2.4	2.4	4.5	3.7	1.0	3.3	2.8	2.7				
Rest of skull .. .	0.0	0.0	0.0	0.0	4.5	1.0	0.6	2.1	3.9	1.4				
Spine (including sacrum) .. .	2.9	0.0	2.4	4.8	4.5	5.0	3.9	2.2	3.0	3.3				
Ribs .. .	0.0	0.0	2.4	2.4	0.0	2.1	2.0	3.2	0.0	1.5				
Clavicle or scapula .. .	0.0	0.0	0.0	4.8	0.0	0.9	0.0	1.1	1.3	0.8				
Pelvis .. .	0.0	2.0	1.5	2.4	6.8	6.1	3.9	3.3	11.3	4.6				
Bones, other than in limbs .. .	5.5	4.0	8.7	16.8	20.4	18.0	19.6	9.1	13.7	14.5	15.8	12.1	33.5	14.3
Bone, unspecified .. .	0.0	0.0	0.0	0.0	2.3	0.0	1.9	0.0	3.8	1.0				
All bones .. .	7.4	20.0	41.5	76.1	54.2	26.9	30.3	23.5	31.4	28.0	50.0	47.8	94.6	38.9

TABLE IX.—Mortality from Primary Tumours of the Bone Associated with Paget's Disease, England and Wales, 1951-3

Site of Primary Tumour	Annual Death Rate per 10,000,000*										
	Males Aged (in Years):							Females Aged (in Years):			
	35-39	40-44	45-49	50-54	55-59	60-64	65-69	45-49	50-54	55-59	60-64
Humerus .. .	0.0	0.0	0.0	0.0	6.4	0.7	1.1	1.1	2.6	0.5	
Femur .. .	1.0	3.5	22.7	3.1	2.7	0.5	2.5	2.5	8.0	1.4	
Tibia or fibula .. .	0.0	1.1	3.5	0.5	1.6	0.2	0.0	0.0	1.3	0.2	
Other limb bones .. .	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
All limb bones .. .	0.0	2.0	2.1	7.6	25.2	44.7	4.5	0.0	7.3	5.3	19.2
Mandible or maxilla .. .	0.0	0.0	1.6	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rest of skull .. .	0.0	0.0	3.2	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Spine (including sacrum) .. .	0.0	0.0	3.2	0.3	1.1	0.0	0.0	0.0	0.0	0.0	0.0
Ribs .. .	0.0	0.0	0.0	0.2	0.0	2.5	0.0	0.0	0.0	0.0	0.0
Clavicle or scapula .. .	0.0	1.1	0.0	0.0	19.8	0.0	1.1	1.1	4.8	0.8	
Pelvis .. .	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
Bones, other than in limbs .. .	0.0	0.0	0.0	7.3	21.7	34.9	3.5	0.0	4.4	0.0	15.5
Bone, unspecified .. .	1.0	1.1	4.7	0.9	0.0	0.0	0.0	0.0	1.2	0.2	
All bones .. .	0.0	4.0	4.2	15.0	52.7	83.2	8.9	0.0	11.8	5.3	37.3

* No deaths were recorded among men under 40 years of age or among women under 50 years of age.

Paget's Disease of Bone

Estimates of the mortality from primary tumours of the bone associated with Paget's disease are given in Table IX. The figures may underestimate the true mortality, as specific inquiries about the presence of Paget's disease were not made and the available information is limited to that provided by the certified cause of death or by the data extracted from the hospital records. The deficiency is, however, unlikely to be great, as tumours associated with Paget's disease are more common in men and the mortality rates from tumours of the limb bones when Paget's disease was not reported were equal in both sexes at ages over 35 years.

No cases were reported with Paget's disease among men under 40 years of age or among women under 50 years of age. After 45 years of age the mortality increased rapidly, and by ages 60–64 years it accounted for over 40% of the total bone tumour mortality. The mean male mortality at ages 40–64 years was nearly three times the mean female mortality, and approximately the same ratio was observed for the two bones most often affected (femur and pelvis) and for all other bones taken together.

Age Distribution

Tables VII and VIII show that there is a peak in the mortality from tumours of the limb bones at ages 15–19 years in both sexes. This peak presumably reflects a peak in incidence several years earlier, and it is reasonable to relate it to the adolescent spurt in growth which is at a maximum at about age 13½ years in boys and 11½ years in girls. At older ages the mortality falls to a minimum in adult life at ages 25–34 years in women and five years later in men; it then rises until at ages 60–64 years the mortality approaches the maximum recorded in late adolescence. This type of distribution is shown by all the principal tumours in the group—that is, by tumours of the humerus, femur, and tibia or fibula. The number of cases recorded for the other limb bones is too few to show whether or not they have a similar bimodal distribution. Examination of Table IX shows that the greater part of the rise in mortality in middle age is due to tumours associated with Paget's disease. The variation of mortality with age in the absence of Paget's disease is illustrated in Fig. 1. In middle age the mortality increases approximately in proportion with the age—a rate of increase which is slower than for any other of the principal types of malignant disease.

Tumours of bones other than the limb bones account for about 30% of the total mortality. Tables VII and VIII show that the mortality rises slowly from birth to ages 20–24 years and then remains fairly steady for the

FIG. 1.—Annual death rate per 10,000,000 persons from primary tumours of the limb bones, excluding cases associated with Paget's disease of bone; by sex and five-year age-group up to age 65 years: England and Wales, 1951-3.

next 20 years. In both sexes, however, the mortality at ages 20–24 years is slightly higher than that at ages 25 to 44 years, and it is possible that the tumours in this group also show an “adolescent peak” in mortality similar to, but much less marked than, that recorded for tumours of the limb bones. If so, it may be noted

FIG. 2.—Annual death rate per 10,000,000 persons from primary tumours of bones, other than limb bones, excluding cases associated with Paget's disease of bone; by sex and five-year age-group up to age 65 years: England and Wales, 1951-3.

that the peak in mortality occurs in the five-year period subsequent to that recorded for tumours of the limb bones and it is possible that this is related to the fact that the bones of the shoulder and pelvic girdles, the thorax, and the spine both begin and end their adolescent growth spurt about a year later than the long bones of the limbs (Tanner, 1961).

At older ages the mortality from tumours of bones other than limb bones rises sharply in men; but it remains constant in women until age 60–64 years, when there is a small increase. The variation of mortality with age in the absence of Paget's disease is illustrated in Fig. 2. The male mortality still rises sharply after age 45 years, but the female mortality now remains practically constant throughout.

Sex Ratio

The data in Tables VII and VIII show that the total mortality from bone tumours is 62% higher among men than among women. The difference is, however, not constant and varies sharply with age, the type of bone, and the presence or absence of Paget's disease. For tumours of the limb bones the male preponderance is greatest when the mortality is at a maximum—that is, 2.1 to 1 at ages 15–19 years—and disappears at ages 0–9 and 30–39 years, when the mortality is low. That this should be so may perhaps be explained by differences in the response of the limb bones to the adolescent growth spurt. At this period the long bones of the limbs increase in length in both sexes; but the increase in length and the relative increase in breadth are substantially greater in boys (Tanner, 1961). As a result it becomes possible in the majority of instances to distinguish a male femur from a female femur after puberty, whereas before puberty they are usually indistinguishable.

At ages 40 years and over the mortality from tumours of the limb bones again becomes higher in males. At this period, however, the excess can be attributed entirely to the occurrence of tumours in relation to Paget's disease. In the absence of Paget's disease the male and female death rates are practically identical (Fig. 1); at ages 30–64 years the mean annual death rates are respectively 22.1 per 10,000,000 men and 20.4 per 10,000,000 women.

For bones other than limb bones death rates are practically equal in both sexes up to the age of 45 years, the mean annual death rates being 12.8 per 10,000,000 men and 12.9 per 10,000,000 women. At older ages the male mortality rises above the female and by ages 60–64

years the ratio of the rates is more than 3 to 1. In this case the male preponderance becomes more marked in the absence of Paget's disease, and the ratio of the rates then rises to more than 4 to 1 (Fig. 2). Tables VII-IX show that the male preponderance is shared by all bones in this group other than the bones of the skull and jaw. The greatest contribution is, however, made by tumours of the ribs and shoulder-girdle. For the tumours, in the absence of Paget's disease, the mean annual death rate at ages 45 to 64 years was seven to eight times higher in men than in women; for tumours of the spine and pelvis it was four times higher.

Histological Type

The study was not intended to provide detailed data for the various pathological types of primary bone tumour, and no attempt was made to standardize the criteria for histological diagnosis. In these circumstances it is not justifiable to estimate the relative frequency of the different tumours. The age-and-sex distribution of cases described as (1) osteosarcoma and (2) chondrosarcoma is given in Fig. 3, which shows that the peak mortality in

FIG. 3.—Relative mortality at different ages under 65 years from osteosarcoma and from chondrosarcoma, by sex: England and Wales, 1951-3.

adolescence is principally due to osteosarcoma; but that there is also a small peak in the mortality from chondrosarcoma. The male excess in chondrosarcoma at ages 45 years and over is due to tumours of the ribs and shoulder-girdle and to a less extent to tumours of the pelvis. Many cases of osteosarcoma and chondrosarcoma must, however, have been omitted because of lack of sufficiently detailed histological information, and these figures cannot usefully be compared with those reported by Price (1955, 1958) from the Bristol Tumour Registry.

Geographical Distribution

Data for the sex-and-age distribution of the population obtained in the 1951 census allow an estimate to be made of the expected number of deaths in different parts of the country. Figures for each county or combination of counties have been compared with the estimated numbers of deaths occurring during the years 1951-3 and are reported elsewhere (Court Brown, Doll, Heasman, and Sissons, 1961). The results fail to provide conclusive evidence of any geographical variation in mortality, although they suggest that there may be a deficit in some parts of Southern England. Data are not, as yet, available to enable a direct comparison to be made between the level of bone-tumour mortality and the total radiation dose received in bone. For this purpose it would be necessary to have a measure of the radioactivity in bones from different parts of the country. A crude comparison between the estimated mortality from primary bone tumours and the radioactivity of the water supplies in 19 counties (Turner, Radley, and Mayneord, 1961) has failed to show any correlation (Court Brown *et al.*, 1961).

Summary

The mortality attributed to primary malignant tumours of bone in England and Wales in 1951-3 has been examined. These years were chosen because 1953 was the year in which the first megaton nuclear bomb was exploded and suitable data were not available for any years before 1951.

Records of deaths attributed to primary malignant tumours of bone in persons aged under 65 years were examined by the General Register Office and a questionnaire was sent to the doctor who signed the death certificate or to the hospital in which the patient had been treated.

Evidence about the nature of the diagnosis was obtained for 990 cases out of a total of 1,169—that is, for 84.7%. In 516 cases (52.1%) the diagnosis of a primary bone tumour was confirmed; in 449 (45.4%) the diagnosis was thought to be not a primary bone tumour, and in 25 (2.5%) the diagnosis was uncertain.

The diagnosis was found to be more reliable: (1) for deaths occurring in hospital (57% confirmed) than for deaths occurring elsewhere (48%); (2) for men (55% confirmed) than for women (48%); (3) for deaths at ages 15-19 years (86% confirmed) than for other ages (40% at ages 45 to 64 years); (4) for deaths attributed to primary tumours of a bone in the lower limb (77% confirmed) than for primary tumours of other bones; and (5) for deaths in which Paget's disease was said to be associated with the tumour (98% confirmed) or, in the absence of Paget's disease, for deaths in which the tumour was specified as being a particular histological type of sarcoma (86%) than for carcinoma or cancer of bone (4%).

The pathological description of the tumour given by the certifying doctor was the most important factor. After it had been allowed for there was still some difference between the reliability of the diagnosis for different bones and, possibly, for deaths occurring at ages 10-24 years and at other ages.

The additional information obtained for 990 deaths allowed an estimate to be made of the proportion of the remaining deaths which were properly attributable to primary tumours of bone. It could then be estimated that 597 deaths from primary bone tumours occurred among persons aged under 65 years in England and Wales during the three years 1951-3. The minimum annual mortality was estimated to be 6.3 per 1,000,000 men and 3.9 per 1,000,000 women. The true figures must be somewhat higher, as some of the 25 deaths in which the diagnosis was uncertain were probably due to bone tumours and some deaths will have been misclassified under other rubrics.

Examination of the sex and age-specific mortality rates attributed to different bones shows that:

(1) The maximum mortality from tumours of the limb bones is recorded in both sexes at ages 15-19 years; at this age the ratio of the male and female rates is also at a maximum (2.1 to 1).

(2) The mortality from these tumours falls from age 20 to 34 years and rises again from age 40 years.

(3) The increase at ages over 40 years is largely due to tumours associated with Paget's disease; the mortality from tumours of the limb bones not associated with Paget's disease increases slowly between ages 35 and 64 years and is equal in both sexes.

(4) The mortality from tumours of bones other than limb bones shows only a faint peak at ages 20–24 years.

(5) At ages under 45 years the mortality is approximately equal in both sexes.

(6) At ages 45 years and over there is a sharp increase in the mortality among men but very little increase among women. In the absence of Paget's disease the discrepancy is more marked and among women the mortality remains practically constant. The male excess in this group is due principally to tumours of the ribs and shoulder-girdle.

No significant difference in the geographical distribution of bone-tumour mortality has been demonstrated.

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APPENDIX

In 25 cases it was impossible to decide whether a primary bone tumour was present. There was no reference to Paget's disease on any of the death certificates. The descriptions of these cases given on the death certificates were:

Case No.	Sex	Age (Yrs.)	Affected Bone	Histological Description	Place of Death
1	M	3	Maxilla	Osteosarcoma	Home
2	M	6	Jaw	Sarcoma	Hospital
3	M	8	Spine	"	Home
4	M	18	Calcis	Ewing's tumour	"
5	M	37	Ilium	Sarcoma	Hospital
6	M	45	Femur	"	Home
7	M	46	Ribs	"	Hospital
8	M	50	Pelvis	Osteosarcoma	Home
9	M	56	Skull	Sarcoma	"
10	M	59	Femur	"	"
11	M	59	Humerus	Malignant neoplasm	"
12	F	9	Lumbar spine	Tumour	"
13	F	23	Fibula	Ewing's sarcoma	"
14	F	26	Ribs	Sarcoma	"
15	F	33	Rib	"	Hospital
16	F	48	Ilium	"	Home
17	F	50	Pelvis	Osteosarcoma	"
18	F	50	"	Chordoma	Hospital
19	F	57	Vertebrae	Sarcoma	"
20	F	60	Ethmoid	"	Home
21	F	60	Rib	"	"
22	F	61	Femur	"	Hospital
23	F	63	Orbit	"	Home
24	F	63	Lumbar spine	Carcinoma	"
25	F	64	Pelvis	Sarcoma	Hospital

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PLEA FOR GREATER USE OF CYTOLOGICAL STUDIES IN EARLY DETECTION OF CANCER

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Among the most important factors influencing the prognosis of malignant disease are the extent of the growth and the degree of its spread. By the time a tumour gives rise to symptoms it may have reached proportions which render treatment difficult and the prognosis poor. The examination of body fluids by the cytological method makes possible the discovery of malignant disease when the tumour is still of microscopic proportions, and thus detection at such an early stage can help to improve prognosis. Furthermore, the method is also of considerable assistance in helping to differentiate malignant disease from other pathological conditions, particularly where other diagnostic tests may be inconclusive.

The cytological method originated in England over 100 years ago, when Walshe (1851) observed fragments of malignant tissue in sputum. From that time onwards other workers, both in this country and elsewhere, carried out much work in this field, and in 1927 Dudgeon and Patrick, experimenting with the wet-fixation technique at St. Thomas's Hospital, examined sputum, urine, and other body secretions for the presence of malignant cells. At about the same time in the United States of America, Papanicolaou (1928) used a similar technique for diagnosing cancer of the female genital tract, and by 1940, having realized the potentialities of the method, he devoted his time wholly to its development, so that to-day, after many years of extensive trial all over the world, it has become inevitably associated with his name and now is used as an everyday routine for cancer detection in most hospitals in the Americas and on the Continent. In Great Britain much excellent cytological work has also been done in a number of centres for some years, but, as Saxton (1960) points out, this country lags far behind both the U.S.S.R. and the U.S.A., where cytological examinations for cancer of the uterus have become routine procedures, and, although in a few localities schemes for this purpose are in operation, he pleads for the establishment of more such schemes in all centres of population where these examinations could be carried out regularly.

Principal Uses of the Cytological Method

Female Genital Tract.—Undoubtedly the most successful application of the cytological method has been its use for the detection of early invasive or pre-invasive carcinoma of the cervix uteri. In Great Britain, Anderson (1950), Wachtel and Plester (1952), Way (1953), McLaren (1953), and Egerton (1957), after trying out the method as a research project, found that their results were so encouraging that they now continue to use it as a routine test in the gynaecological clinics of the hospitals where they work. Wrigley (1960) maintains that it is essential as an additional means of investigation where there is the slightest sign or suspicion