carried out until long after stopping paracetamol, it remains possible that an acquired toxic effect due to chronic drug ingestion had been corrected. Alternatively, our patient may have lacked other protective factors.[1,16]

The exact role of paracetamol in the causation of "cryptogenic" chronic hepatitis or cirrhosis is not clear. Patients presenting with this picture should be questioned about the ingestion of paracetamol in any of the many products containing this agent.[3] Paracetamol hepatoxicity may occur without deliberate overdose or other indiscretion of intake, and may present as, or progress to, chronic active hepatitis.

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REFERENCES

1. *Lancet*, 1975, ii, 1189.
2. *Med. Lett. Lond.* 1976, **18**, 73.
3. Ameer, E., Greenblatt, D. J. *Ann. intern. Med.* 1977, **87**, 202.
4. Clark, R., Bonirakchanyavat, V., Davidson, A. R., Thompson, R. P. H., Widdop, B., Goulding, R., Williams, R. *Lancet*, 1973, i, 66.
5. Johnson, G. K., Tolman, K. G. *Ann. intern Med.* 1977, **87**, 302.
6. Beutler, E., Duron, O., Kennedy, B. J. *J. lab. clin. Med.* 1963, **61**, 882.
7. Lowry, O. H., Rosebrough, N. J., Farr, A. L., Randall, R. J. *J. biol. Chem.* 1951, **193**, 265.
8. Brodie, B. B., Axelrod, J. *J. Pharmac. exp. Ther.* 1949, **95**, 58.
9. Howie, D., Adriaenssens, P. I., Prescott, L. F. *J. Pharm. Pharmac.* 1977, **29**, 235.
10. Buckpitt, A. R., Rollins, D. E., Nelson, S. D., Franklin, R. B., Mitchell, J. R. *Analyt. Biochem.* 1977, **83**, 168.
11. Mitchell, J. R., Thorgeirrson, S. S., Potter, W. Z., Jollow, D. J., Keiser, H. *Clin. Pharmac. Ther.* 1974, **16**, 676.
12. Prescott, L. F., Wright, N. *Br. J. Pharmac.* 1973, **49**, 602.
13. Dixon, M. F., Nimmo, J., Prescott, L. F. *J. Path.* 1971, **103**, 225.
14. Boyd, E. M., Hogan, S. E. *Can. J. Physiol. Pharmac.* 1968, **46**, 239.
15. Boyland, E., Chasseaud, L. F. *Adv. Enzymol.* 1969, **32**, 173.
16. Mitchell, J. R., Hinson, J. A., Nelson, S. D. *in* Glutathione: Metabolism and Function (edited by I. M. Arias and W. B. Jakoby); p. 357. New York, 1976.

Preliminary Communications

MORTALITY FROM LEUKÆMIA AND CANCER IN SHIPYARD NUCLEAR WORKERS

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Summary A review of death certificates in New Hampshire, Maine, and Massachusetts for 1959–77 yielded a total of 1722 deaths among former workers at the Portsmouth Naval Shipyard where nuclear submarines are repaired and refuelled. Next of kin were contacted for 592. All deaths under age 80 were classified as being in former nuclear or non-nuclear workers depending on information supplied by next of kin. With U.S. age-specific proportional cancer mortality for White males as a standard, the observed/expected ratio of leukæmia deaths was 5·62 (6 observed, 1·1 expected) among the 146 former nuclear workers. For all cancer deaths, this ratio was 1·78. Among non-nuclear workers there was no statistically significant increase in proportional mortality from either leukæmia or from all cancers. The excess proportional leukæmia and cancer mortality among nuclear workers exceeds predictions based on previous data of radiation effects in man.

INTRODUCTION

THIS study was prompted by a case referred to T.N. The patient was a 63-year-old male with pancytopenia and splenomegaly. Bone-marrow biopsy and splenectomy with electronmicroscopy confirmed hairy-cell leukæmia. The patient had been a nuclear welder at the Portsmouth Naval Shipyard (P.N.S.) from 1959 to 1965. The shipyard reported that his total radiation exposure was about 1–2 rem for his 6 years of nuclear work. The patient mentioned that some of his fellow nuclear workers (all younger than he) had died.

Follow-up studies on people exposed to ionising radiation—notably, survivors of the Hiroshima and Nagasaki A bombs, radiologists, Marshallese Islanders, and patients exposed to X-rays for medical purposes—are remarkably consistent in the estimates they yield of the dosage effects of radiation in causing disease. One summary of radiation effects on man[1] estimates that an extra total lifetime dose of 0·1 rem above natural background radiation, if given to the entire U.S. population, would cause about 100 extra cancer deaths per year for about 20 years after the exposure.

Little work has been done on people occupationally exposed to chronic, low levels of radiation and to radioactive materials. High internal radiation doses—after inhalation or ingestion of radioactive materials or absorption of contaminants through cuts in the skin, for example—could cause tissue damage which would be poorly predicted by external gamma ray detectors. Mancuso et al.[2] studied 3520 deaths among former nuclear workers at the Hanford Works in Richland, Washington, and estimated that the radiation dose necessary to double mortality from neoplasms of the reticuloendothelial system and leukæmia was less than 10 rem.

Can the results of studies on A-bomb survivors and persons exposed to medical X-rays be applied to occupational exposure to radioactivity? We have studied proportionate mortality from cancer and leukæmia in a group of workers in the U.S. Naval Nuclear Propulsion Program.

METHODS

The P.N.S. employs about 7500 people, and since 1959, when nuclear work began, it has employed 20 000 people. Within many occupations—such as welder, electrician, pipefitter, or mechanic—there is a clear division between those who do exclusively non-nuclear work and those who do both non-nuclear and nuclear work, the work being similar except for exposure to radiation, mostly during repair and refuelling of the atomic reactors on nuclear submarines.

We estimate the total number of nuclear workers at the P.N.S. since 1959 to be between 3000 and 5000, or roughly 20% of the workforce.

Death certificates for the years 1959–77 for New Hampshire, Maine, and Massachusetts were reviewed and from those indicating occupation at the P.N.S. or the Kittery Naval Yard, the name, occupation, death certificate number, dates of birth and death, age at death, name of physician treating patient or completing death certificate, name and address of next of kin or informant, and cause(s) of death were copied. From over

TABLE I—OBSERVED (O) AND EXPECTED (E) CANCER DEATHS FOR NUCLEAR AND NON-NUCLEAR WORKERS BY AGE AND PERIOD OF DEATH

	Nuclear				Non-nuclear			
		Cancer				Cancer		
	All deaths	O	E	O/E	All deaths	O	E	O/E
Total	146	56	31·5	1·78	379	88	79·7	1·10
Age (yr):								
<50	16	4	2·7	1·46	20	6	3·2	1·85
50–59	47	11	10·4	1·06	56	9	12·5	0·72
60–69	52	31	12·1	2·56	134	34	31·1	1·09
70–79	31	10	6·3	1·60	169	39	32·9	1·19
Period of death:								
1959–64	7	3	1·5	2·03	18	2	3·8	0·52
1965–69	26	10	5·6	1·79	108	28	23·3	1·20
1970–74	70	27	15·3	1·77	163	39	34·1	1·14
1975–77	43	16	9·1	1·76	90	19	18·4	1·03

100 000 death certificates 1722 deaths of former P.N.S. workers were identified.

A team of workers looked up telephone numbers and called the next of kin, working from lists on which the causes of death were concealed. They asked the following questions: "Did you know the deceased?", "Did he work at the P.N.S.?", "Did he work with radiation or wear a radiation badge while working?", and "What was the cause of death?" (this information was used to ascertain agreement between what appeared on the death certificate and the responses of the informants). From the list of 1722 deaths the team was able to contact and obtain information from next of kin of 592, or about a third, of the deceased workers.

One of us (T.N.) classified the causes of death from the death certificates as cancer (subdivided into leukæmia, other neoplasms of lymphatic and hæmatopoietic tissue, or other) or non-cancer, but without knowing whether the deceased had been engaged in nuclear work or not.

If the next of kin's response to the question about radiation or wearing of radiation badge was "yes" or "probably yes" the deceased's work was classified as nuclear. If the answer was "no" or "do not know" the work was classified as non-nuclear, the numbers being 146 and 446, respectively. Since there were no deaths among nuclear workers at age 80 and above, we restricted our analysis to those under 80. This reduced the number of deaths among non-nuclear workers to 379.

Nearly all the deceased workers were White males. Indirect age-adjustment was used. Expected deaths by cause were calculated by applying the age-specific proportional mortality-rates (in 5-year intervals) for U.S. White males in 1973[3] and then summing over the age range.

RESULTS

Table I indicates the observed and expected number of cancer deaths among the workers: observed cancer deaths among nuclear workers at P.N.S. exceed by more than 75% those expected based on the U.S. White male experience ($P<0.00001$). Among non-nuclear workers the increase in cancer deaths is only 10% ($P>0.05$). Among nuclear workers the excess of cancer deaths is most distinct among those aged 60–69 ($P<0.00001$). Increased cancer deaths were noted in other age-groups of nuclear workers, but none of these increases achieved statistical significance. When examined by period of death, the excess of observed over expected cancer deaths is remarkably consistent (table I).

Table II shows the cancer deaths in more detail. Although the numbers are small, a striking feature is the excess of leukæmia deaths among the nuclear workers.

Our team of interviewers contacted only 525 (36·2%) of next of kin of 1450 former P.N.S. workers who had died below the age of 80. For all workers, however, we knew the age, year, and cause of death, so we classified all 1450 deaths as cancer or non-cancer (but not as nuclear or non-nuclear because we did not know this for the 925 men whose next of kin had not been contacted). To determine if, in the study group, we had selected particularly for cancer deaths we calculated contact-rates (table III).

There was a slight tendency to increased contact-rates of next of kin for cancer deaths (39%) than for non-cancer deaths (35%), but this difference is not significant and any bias from this source cannot have been strong. The study group included 8 of the 20 (40%) leukæmia deaths, 10 out of the 25 (40%) deaths from other neoplasms of lymphatic and hæmatopoietic tissues, and 126 of 521 (39%) of all other cancer deaths, so selection for

TABLE II—OBSERVED AND EXPECTED CANCER DEATHS AMONG NUCLEAR AND NON-NUCLEAR WORKERS BY TYPE OF CANCER

Malignancy	Nuclear			Non-nuclear		
	O	E	O/E	O	E	O/E
Leukæmia	6	1·1	5·62	2	2·8	0·71
Other neoplasms of lymphatic and hæmatopoietic tissues	4	1·8	2·26	6	4·3	1·41
All other malignant neoplasms	46	28·6	1·61	80	72·6	1·10
Total	56	31·5	1·78	88	79·7	1·10

TABLE III—PERCENTAGES OF CANCER AND NON-CANCER DEATHS WHERE NEXT OF KIN WERE CONTACTED

Period	No. of deaths		% of next of kin contacted		
	Cancer	Non-cancer	Cancer	Non-cancer	Difference
1959–77	366	1084	39·3	35·1	4·2
1959–64	44	153	11·4	13·1	−1·7
1965–69	100	288	38·0	33·3	4·7
1970–74	160	465	41·3	35·9	5·4
1975–77	62	178	56·5	55·1	1·4

TABLE IV—OBSERVED AND EXPECTED CANCER DEATHS BY TYPE OF CANCER AMONG 925 WORKERS WHOSE NEXT OF KIN WERE NOT CONTACTED

Malignancy	O	E	O/E
Leukæmia	12	6·9	1·74
Other neoplasms of lymphatic and hæmatopoietic tissues	15	10·6	1·42
All other malignant neoplasms	195	175·6	1·11
Total	222	193·0	1·15

deaths from leukæmia or lymphatic and hæmatopoietic malignancies can also be ruled out.

Those whose next of kin we were unable to contact would have formed a mixture, of unknown proportions, of nuclear and non-nuclear workers, so we would expect the observed/expected ratios for deaths due to malignancy to lie between those for known nuclear and non-nuclear workers shown in table II. Table IV shows that this was so.

DISCUSSION

The increased numbers of cancer and leukæmia deaths among Naval nuclear shipyard workers seem out of proportion to predictions based on prior knowledge of the effects of ionising radiation in man. Previous data suggest that 50–100 rem doubles leukæmia mortality and 300–400 rem doubles the number of total cancer deaths. Radiation records from the shipyard were not available to us, but radiation doses seem to have been well within national occupational safety standards. Information provided by 50 past and present P.N.S. nuclear workers suggested total radiation doses of less than 10 rem lifetime. Within the Naval Nuclear Propulsion Program the mean radiation exposure for the industrial workers at risk (which includes the shipyard workers) was 0·211 rem annually.[4] The nuclear workers at the P.N.S. had six times the proportional mortality of leukæmia and twice the proportional mortality for all cancers expected for U.S. White males of the same age-groups. These increased figures were found with radiation doses that probably averaged less than 10 rem total lifetime exposure as measured by workers' film badges.

Possible reasons for this discrepancy are:

(1) There may have been systematic error or bias in the information supplied by next of kin.

(2) The badges may not have accurately reflected the external radiation exposure.

(3) Internal emitters may have caused high internal radiation doses which were not picked up by external detectors.

(4) Other factors (asbestos, smoking, industrial solvents) may have interacted synergistically with radiation to cause more deaths from cancer and leukæmia than radiation alone would have caused.

(5) Some workers may have been exposed to much larger doses (e.g., in a radiation accident) than the badges indicated.

(6) If internalised particulate radiation from fall-out caused most of the leukæmias and cancers in A-bomb survivors, rather than the higher external dose from blast, this would explain, in part, why the predicted amounts of cancer and leukæmia per rem total exposure from A-bombs underestimated the internalised effects from occupational exposure to radioactive materials.

There are two other important limitations of this study. Firstly, it was an analysis of deaths only; no information was available to us on the total population at risk. Secondly, we had no information on the length of time the workers worked at the shipyard, how long the nuclear workers were exposed to radiation, and the amounts of radiation that they received. All the same, we believe that our finding of increased proportional mortality of cancer and leukæmia at probably low occupational radiation exposure levels, while not proving a risk, ought to prompt more careful and thorough cohort studies of workers in naval yards where nuclear-powered vessels are serviced.

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REFERENCES

1. The Effects on Populations of Exposure to Low Levels of Ionising Radiation. U.S. Government Printing Office, 1972.
2. Mancuso, T. F., Stewart, A., Kneale, G. *Hlth Phys.* 1977, **33**, 369.
3. The Vital Statistics of the United States 1973; vol. II, mortality. U.S. Government Printing Office, 1975.
4. Klement, A. W., and others. Estimates of Ionising Radiation Doses in the United States, 1960 to 2000. U.S. Environmental Protection Agency, 1972

LEUCOCYTE ADHERENCE INHIBITION FOR DETECTING SPECIFIC TUMOUR IMMUNITY IN EARLY PANCREATIC CANCER

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Summary Tumour-specific immunity to pancreatic tumour antigens, assayed by an automated tube leucocyte-adherence inhibition assay (L.A.I.), was detected in 3 of 3 patients with localised pancreatic cancer and 3 of 8 patients with more extensive pancreatic cancer. Leucocytes from pancreatic cancer patients with L.A.I. reactivity did not react to antigens of stomach, colon, or lung tumours; leucocytes from patients with stomach, colon, or lung cancer or inflammatory disease of the pancreas and bowel did not show L.A.I. reactivity to pancreatic tumour antigens.

INTRODUCTION

THE frequency of pancreatic cancer, the second most common gastrointestinal neoplasm, is increasing in incidence at a rate exceeded only by that of lung cancer.[1] The highest reported 5-year survival-rate is 18%, and surgical resection is the only cure.[2] In animal tumour models, tumour immunity is detectable when the tumour-cell number is small; the cancer is then potentially curable.[3] The tube leucocyte-adherence inhibition assay in human cancer (L.A.I.)[4,5] is a reliable and rapid assay of tumour-specific immunity;[6–12] sensitised leucocytes from patients with tumours, but not leucocytes from unsensitised tumour patients or controls, after in vitro incubation with extracts of tumours of the same organ and same histological type, lose their former ability to adhere to glass surfaces.[13,14] This study was undertaken to determine if an automated L.A.I. assay could detect specific tumour immunity in early pancreatic cancer.

PATIENTS

In the test group, 11 patients had carcinoma of the pancreas, 10 had pancreatitis (3 with pancreatic pseudocysts), 1 had islet-cell adenoma, 1 had cancer of the duodenum, and 2 had cancer of the ampulla of Vater. Controls were 34 patients with elective surgical problems, 15 with colonic cancer, 6 with other malignancies, 8 with cholecystitis, 8 with Crohn's disease, 6 with ulcerative colitis, and 8 with diverticular disease.

Pancreatic cancer was divided (arbitrarily) into two groups; limited disease was defined as a lesion <5 cm with no affected lymph-nodes; in advanced disease, lesions were >5 cm with or