

Parkinson's disease and Alzheimer's disease: hypersensitivity to X rays in cultured cell lines

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SUMMARY Fibroblast and/or lymphoblastoid lines from patients with several inherited primary neuronal degenerations are hypersensitive to DNA-damaging agents. Therefore, lymphoblastoid lines were irradiated from patients with sporadic Parkinson's disease (PD), Alzheimer's disease, and amyotrophic lateral sclerosis. The mean survival values of the eight Parkinson's disease and of the six Alzheimer's disease lines, but not of the five amyotrophic lateral sclerosis lines, were less than that of the 28 normal lines. Our results with Parkinson's disease and Alzheimer's disease cells can be explained by a genetic defect arising as a somatic mutation during embryogenesis, causing defective repair of the X-ray type of DNA damage. Such a DNA repair defect could cause an abnormal accumulation of spontaneously occurring DNA damage in Parkinson's disease and Alzheimer's disease neurons *in vivo*, resulting in their premature death.

Recent studies have identified a group of disorders which have hypersensitivity *in vitro* to DNA-damaging agents and the neuropathological features of a primary neuronal degeneration.¹ Xeroderma pigmentosum is an autosomal recessive disease with inherited defects in mechanisms for repairing DNA damaged by ultraviolet radiation.^{1,2} Some xeroderma pigmentosum patients have a primary neuronal degeneration involving principally the pyramidal cells of the cerebral cortex, the Purkinje cells of the cerebellum, the deep nuclei of the basal ganglia and cerebellum, the zona compacta of the substantia nigra, and the locus ceruleus.¹⁻⁵ In advanced cases the spinal cord pathology resembles that of Friedreich's ataxia.⁵ The degree of *in vitro* sensitivity of cultured xeroderma pigmentosum fibroblast and lymphoblastoid cell lines to the lethal effects of ultraviolet radiation correlates with the age of onset and severity of neurological signs in this disease.^{1,4,6-8} Because of these findings we proposed that the primary neuronal degeneration in xeroderma pigmentosum results from the *in vivo*

accumulation in neurons of unrepaired DNA damage.^{1,2,4,6,9-11} This DNA-damage hypothesis was expanded to include other DNA-damaging agents and primary neuronal degenerations.^{1,9,10,12,13} Consistent with this hypothesis, hypersensitivity to the lethal effects of ionising radiation and/or radiomimetic chemicals has been found in cultured cells from patients with ataxia telangiectasia,^{12,14-19} Friedreich's ataxia,²⁰ Huntington's disease,^{12,15,16,21-24} and familial dysautonomia.²⁴ We now report that lymphoblastoid lines from patients with Parkinson's disease and Alzheimer's disease, but not those from patients with amyotrophic lateral sclerosis, are hypersensitive to X-rays. A preliminary report of some of these findings has been published.¹³

Methods

Origins of normal and patient lymphoblastoid lines. Lymphoblastoid lines are Epstein-Barr virus-transformed peripheral blood B lymphocytes which grow as immortal lines in suspension culture. With the exception of two normal lines, all normal and patient lines were established at the Institute for Medical Research, Camden, NJ. A total of 28 normal lymphoblastoid lines were studied from donors who were not known to have any neurological disease. Their age and sex, as well as the designation and post-X-ray survival of their cell lines, have been presented previously.²⁵ The mean age at venepuncture for obtaining blood for establishment of the lines from 27 of these donors (the

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Table 1 Designations, derived lymphoblastoid lines, viability ratios, and clinical features of Parkinson's disease patients

Patient	Age*	Sex	Cell line	Viability ratio†	Clinical features									Response to anti-Parkinsonian drugs
					Bradykinesia	Rigidity	Tremor	Akinesia	Shuffling gait	Changed handwriting	Decreased eye blinking	Decreased facial expression	Decreased associated movements	
PD1FABE	71	M	RB 3937	0.43	+	+	+				+			+
PD2FABE	52	M	RB 3971	0.45	+	+	+			+				+
PD3FABE	60	M	RB 3973	0.50	+	+	+				+	+		+
PD4BE‡	64	F	RB 4642	0.43	+	+	+		+	+			+	+
PD5FABE	53	M	RB 5288	0.48		+	+	+	+			+	+	+
PD6BE	64	M	RB 5828	0.48	+	+	+	+						+
PD7BE	65	M	RB 5860	0.45	+	+	+		+	+				+
PD8BE	63	M	RB 6041	0.50	+	+	+		+		+	+	+	+

*Age at venepuncture for obtaining blood for establishment of lymphoblastoid lines.

†For 100 rads of X-rays; each ratio is the mean of at least six replicate experiments and is calculated as described in Materials and Methods.

‡Mother had PD.

PD Parkinson's disease. FA Fargo, North Dakota. BE Bethesda, Maryland. + known to be present.

age of one donor was not known) was 44.0 years (range, 12 to 71 years), and their ages represented every decade from the second to the eighth decade of life. The 11 oldest of the 27 normal donors had a mean age of 62.8 years (range, 54 to 71 years). The two lines (E1, R1) established in our laboratory were from donors who had not received any formal clinical evaluation. The 14 normal lines with the 'GM' prefix in their designations were from donors whose blood had been acquired by the NIGMS Human Genetic Mutant Cell Repository at the Institute for Medical Research and are described in the Institute's catalogue of cell lines. Twelve normal donors, who were extensively screened at the National Institutes of Health, comprised the NIH normal donor series, and their cell lines carry the 'RB' prefix in their designations. Each of these 12 donors was required to submit a complete medical history and undergo a physical examination, screening blood tests, urinalysis, electrocardiogram, chest radiography, and a detailed neurological examination conducted by a neurologist (RJP). None had symptoms or signs of any active illness. Extensive family pedigrees spanning several generations were constructed. Subjects were excluded from the NIH normal donor series if there was any family history of neurological disorder.

Lymphoblastoid lines from eight Parkinson's disease patients were studied. The identification and clinical features of these patients are presented in table 1. The Parkinson's disease patients had a mean age of 61.5 years (range, 52 to 71 years). Each patient had a gradual onset of cogwheel rigidity, resting tremor, and/or bradykinesia. Associated symptoms in some patients included shuffling gait, akinetic episodes, change in handwriting, decreased eye blinking, masked facies, and lack of associated movements. All patients showed symptomatic improvement in response to treatment with anti-Parkinsonian medication. Patients with evidence of motor neuron disease, cerebellar signs, dysautonomic syndrome, gaze limitation, profound dementia, or a history of exposure to drugs or toxic substances known to produce Parkinsonism were excluded from this study. Patient PD4BE was considered to have familial Parkinson's disease, since she had a first degree relative (mother) with this disease.

The six Alzheimer's disease patients (table 2) had a mean age of 62.5 years (range, 58 to 69 years). All

Alzheimer's disease patients had cognitive dysfunction which began insidiously before 65 years of age. Progressive intellectual deterioration had been present for at least one year prior to neurological evaluation. No patient had a history of stroke-like episodes or a known disorder associated with central nervous system involvement. Diffuse cerebral atrophy and ventricular dilatation were observed in all Alzheimer's disease patients by computed tomographic scan. After a complete medical and neurological evaluation, no other cause for the dementia was found. One patient (AD1BE) is an index case of an extensive pedigree of histologically confirmed familial Alzheimer's disease.²⁶

The five patients with amyotrophic lateral sclerosis (table 2) had an inexorably progressive disease characterised by muscle weakness and wasting. They had clinical (fasciculations and atrophy) and electromyographic (fibrillations and large polyphasic motor units) evidence of denervation in muscles of both the upper and lower extremities. Nerve conduction velocity was normal. Upper

Table 2 Designations, derived lymphoblastoid lines, and viability ratios of Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis patients

Patient	Age* (yr)	Sex	Cell line	Viability ratio†
AD1BE	58	F	RB 4160	0.50
AD2BE	59	F	RB 4964	0.45
AD3BE	61	F	RB 5054	0.47
AD4BE	69	F	RB 5176	0.46
AD5BE	67	M	AG 6204	0.51
AD6BE	60	F	AG 6868A	0.44
MS1FABE	56	M	RB 3939	0.57
MS2FABE	52	M	RB 3975	0.52
MS3FABE	59	F	RB 4001	0.50
MS4FABE	56	M	RB 4003	0.53
MS5FABE	31	M	RB 5362	0.53
ALS1FABE	68	M	RB 4073	0.56
ALS2FABE	72	M	RB 4075	0.50
ALS3FABE	40	F	RB 4532	0.55
ALS4FABE	—	M	RB 4607	0.62
ALS5FABE	65	M	RB 5698	0.48

*As in table 1; age of patient ALS4FABE is unknown.

†As in table 1.

AD Alzheimer's disease. BE Bethesda, Maryland. MS Multiple sclerosis. FA Fargo, North Dakota. ALS amyotrophic lateral sclerosis.

motor neuron signs (hyperreflexia and extensor plantar responses) were also present. There were no sensory abnormalities or cerebellar or extrapyramidal signs. The five patients with multiple sclerosis (table 2) were diagnosed on the basis of multiple exacerbating and remitting central nervous system signs and symptoms and fit the diagnostic criteria for clinically definite multiple sclerosis (CDMS A1).²⁷

Tissue culture methods, irradiation with X-rays, and viability determination. Culturing, irradiation, and viability determination were performed as in previous experiments^{8, 12, 17, 18} and as described in detail elsewhere.²⁵ For experiments in which only 100 rads of X-rays were to be administered, the stock cell suspensions were diluted with fresh culture medium to a final concentration of 2×10^5 viable cells/ml. For the dose-response experiments, each line's stock cell suspension was centrifuged at 600 g just prior to irradiation, and the cells were resuspended at a final concentration of 3×10^5 viable cells/ml of fresh culture medium. The cell lines were irradiated at room temperature at 126 rads/min with a 235-kVp X-ray machine. Concentrations of viable (that is, trypan-blue dye-excluding) cells in unirradiated and irradiated cultures were determined on the third postirradiation day using coded samples to eliminate any possibility of observer bias. **Ultraviolet irradiation.** The experiments were performed as described above except that after centrifugation the cells were resuspended at a final concentration of approximately 4×10^6 viable cells/ml of Hanks' balanced salt solution (without phenol red). Some of the resuspended cells were then irradiated with 254-nm ultraviolet irradiation at a flux of 0.08 J/m² from a germicidal lamp (General Electric No G15T8). Immediately after the time of irradiation, each cell suspension was diluted with seven volumes of fresh medium, and the irradiated and unirradiated cells were incubated for three days when the viable cells were determined by the dye-exclusion method.

Computation of viability ratio. A line's postirradiation viability ratio was calculated by dividing the concentration of viable cells in an irradiated culture on the third postirradiation day by the concentration of viable cells in an unirradiated culture of the same line on the third day. Thus, calculation of the viability ratio automatically corrects for differences in unirradiated growth rates among the cell lines, as described in detail previously.^{8, 25} Experiments in which the viable cells in the unirradiated culture had not tripled in concentration by the third day were discarded. There was no correlation between the postirradiation viability ratios of either normal or patient lines and the lines' unirradiated growth ratios or the ages or sexes of the cell donors. The three-day unirradiated growth ratios \pm standard error of the Parkinson's disease (5.0 ± 0.4) and Alzheimer's disease (5.7 ± 0.7) lines were not significantly different from that (5.6 ± 0.3) of the normal lines ($p \geq 0.25$). Comparisons of disease groups with the normal group are based on the standard *t* test for comparing independent means,²⁸ and two-sided *p* values are reported.

Validation of the survival assay and viability ratio. Ataxia telangiectasia is a recessively inherited primary neuronal degeneration.^{29, 30} As cited and reviewed elsewhere,²⁵ several investigators have compared the post-ionizing-radiation colony-forming ability of ataxia telangiectasia

homozygote and heterozygote fibroblast and lymphoblastoid lines with that of normal lines. The survival of fibroblast lines has ranged from 30 to 45% of normal for ataxia telangiectasia homozygote lines and from 74 to 90% of normal for ataxia telangiectasia heterozygote lines. For lymphoblastoid lines the reported values were 36 and 80%, respectively.¹⁴ The relative survival based on viability ratios currently obtained with our lymphoblastoid line survival assay, 50% for ataxia telangiectasia homozygote (GM 717, 1526, 3189) and 75% for ataxia telangiectasia heterozygote (GM 3187, 3188) lines, are in good agreement with these published data based on colony forming ability. The validity of the viability ratio as a measure of cell survival after ultraviolet irradiation treatment of xeroderma pigmentosum and Cockayne syndrome lymphoblastoid lines has also been proven: the lines' viability ratio^{8, 31} have the same relative survival as do the colony-forming abilities of the patients' fibroblast lines.^{6, 7, 32}

Results

Post-X-ray survival. Dose-response curves were obtained for one ataxia telangiectasia line (fig 1A), two Parkinson's disease lines (fig 1B), two Alzheimer's disease lines (fig 1C), and three lines from normal donors who were age-matched with the Parkinson's disease and Alzheimer's disease donors (fig 1A). The three normal lines had similar survival curves. The ataxia telangiectasia line had a marked hypersensitivity to X-rays. Although the Parkinson's disease and Alzheimer's disease lines were less sensitive than the ataxia telangiectasia line to the lethal effects of X-rays, the Parkinson's disease pair, as well as the Alzheimer's disease pair, had lower survival at each of the doses tested than the normal lines ($p < 0.05$).

Additional experiments were performed, using a radiation dose of 100 rads, to compare the post-X-ray survival of all the patient lines with that of all the normal lines (fig 2). The post-X-ray viability ratios of all 28 normal lines is shown in the first column. The mean viability ratio \pm standard error for the five multiple sclerosis lines (0.530 ± 0.011) and that for the five amyotrophic lateral sclerosis lines (0.542 ± 0.025) did not differ significantly from the mean ratio of 0.537 ± 0.009 of the normal group (fig 2) ($p > 0.40$). The eight Parkinson's disease lines (seven sporadic, one familial) had a mean viability ratio of 0.465 ± 0.010 . The familial Parkinson's disease line (RB 4642) had a viability ratio of 0.43 which is one of the lowest in the Parkinson's disease group (Θ , fig 2). When the mean viability ratio of either all eight Parkinson's disease lines or the seven sporadic Parkinson's disease lines was compared to that of the normal group, each Parkinson's disease group had a significantly lower post-X-ray survival

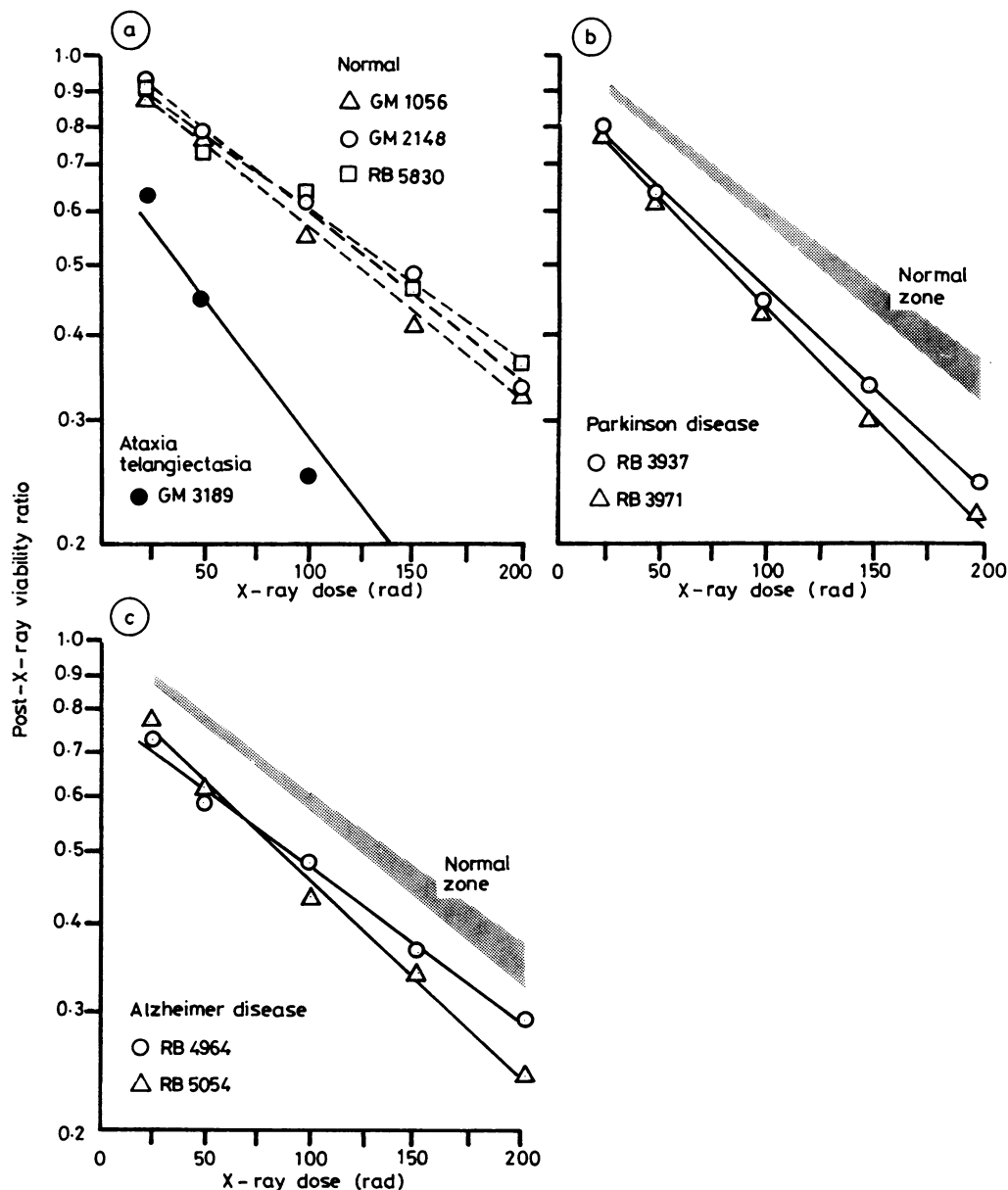


Fig 1 Dose-response survival curves for normal and representative patient lymphoblastoid lines after treatment with X-rays. (A) Normal cell lines and ataxia telangiectasia (AT) line. (B) Parkinson's disease lines. (C) Alzheimer's disease lines. The shaded "normal zone" of B and C encompasses the survival curves of the three normal lines in A. The one male and two female normal donors were 65, 54, and 65 years of age, respectively. The age and sex of the Parkinson's disease and Alzheimer's disease donors are shown in tables 1 and 2, respectively. Each plotted data point for a cell line is the mean viability ratio obtained from six replicate experiments performed at the indicated X-ray dose. The exponential portion of each survival curve was not fitted to the plotted data points but was determined, as described previously,⁴¹ by averaging the slopes and intercepts calculated from the six replicate experiments performed on each line. Although the viability ratios of the ataxia telangiectasia disease line at the 150 and 200 rad doses are not shown, they were used in calculating the slope of the exponential portion of its survival curve.

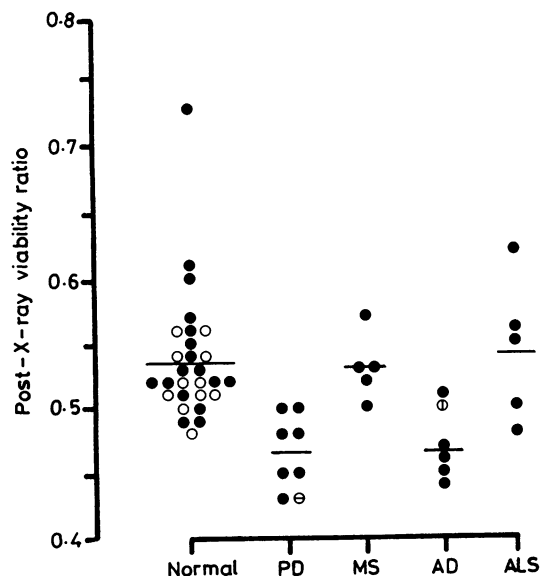


Fig 2 Survival of lymphoblastoid lines treated with 100 rads of X-rays. Each symbol represents the mean viability ratio of at least five replicate experiments on each normal and at least six replicate experiments on each patient line. A total of 280 experiments were performed on the normal, 65 on the Parkinson's disease (PD), 36 on the multiple sclerosis (MS), 53 on the Alzheimer's disease (AD), and 31 on the amyotrophic lateral sclerosis (ALS) lines. Each horizontal bar represents the mean ratio for its group. Omission of the highest normal line, whose viability ratio of 0.73 increases the variance of the normal group of 0.530 ± 0.006 and in lower p values for the Parkinson's disease and Alzheimer's disease groups ($p \leq 0.0002$). Open circles = lines from the 11 oldest normal donors whose ages are similar to those of the Alzheimer's disease and Parkinson's disease patients; \ominus = line from the patient with familial Parkinson's disease; \oplus = line from the patient with familial Alzheimer's disease.

($p = 0.0004$ and 0.0001 , respectively). The six Alzheimer's disease lines (five sporadic, one familial) had a mean viability ratio of 0.472 ± 0.011 . The familial Alzheimer's disease line (RB 4160) had a viability ratio of 0.50 which is near the top of the Alzheimer's disease group (\oplus , fig 2). When the mean viability ratio of either all six Alzheimer's disease lines or the five sporadic Alzheimer's disease lines was compared to that of the normal group, each Alzheimer's disease group had significantly lower post-X-ray survival ($p = 0.004$). The lines (open symbols) from the 11 oldest normal donors, whose mean age is similar to that of the Parkinson's disease and Alzheimer's disease donors, had a mean viability ratio of 0.523 ± 0.008 which was

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Post-ultraviolet irradiation survival. The eight normal lymphoblastoid lines studied had a mean post-ultraviolet irradiation viability ratio of 0.68 ± 0.03 (data not shown). The post-ultraviolet irradiation survival was determined for three Parkinson's disease lines (RB 3971, 3937, 5860) and three Alzheimer's disease lines (RB 4160, 5050, 5176) (data not shown). Their mean post-ultraviolet irradiation viability ratios were, respectively, 0.73 ± 0.04 and 0.66 ± 0.03 and did not differ significantly from the mean post-ultraviolet irradiation viability ratio of the eight normal lines ($p > 0.30$).

Discussion

Alzheimer's disease and Parkinson's disease are both progressive degenerations of the central nervous system occurring in the elderly.^{29,33} Both Alzheimer's disease^{26,29,33} and Parkinson's disease^{29,33,34} are sporadic disorders, although occasional cases of Alzheimer's disease manifesting autosomal-dominant inheritance have been reported.²⁶ In Alzheimer's disease there is progressive loss of neurons in the cerebral cortex,^{29,33} basal forebrain,³⁵ and locus ceruleus.^{29,36} In Parkinson's disease there is progressive loss of neurons in the substantia nigra,²⁹ basal forebrain,³⁷ and locus ceruleus,^{29,33} and some demented Parkinson's disease patients have neuropathological features which are indistinguishable from those of Alzheimer's disease.³⁷ There has so far been no pathophysiological explanation for the neurodegeneration in either Parkinson's disease or Alzheimer's disease.

Recent studies have suggested that some disorders associated with a primary neuronal degeneration have hypersensitivity to DNA-damaging agents.¹ The first of these disorders to be so identified³⁸ was xeroderma pigmentosum, an autosomal recessive disease with inherited defects in the repair of the ultraviolet irradiation-type of DNA-damaging agent,^{1,2} resulting in severe actinic degeneration of sun-exposed skin.^{2,11} Some xeroderma pigmentosum patients develop a relentlessly progressive primary neuronal degeneration, usually in childhood,^{1-3,5,6} but occasionally as late as the fourth decade.⁴ Neuronal loss occurs in several sites,^{1,2,5} including some of those affected in Alzheimer's disease and/or Parkinson's disease, namely the locus ceruleus and substantia nigra. There is hypersensitivity to ionizing radiation and radiomimetic DNA-damaging chemicals in cells from patients with the primary neurodegenerations of ataxia telangiectasia,^{12,14-19} Huntington's disease,^{12,15,16,21-24}

Friedreich's ataxia,²⁰ and familial dysautonomia.²⁴ However, some primary neuronal degenerations may have no hypersensitivity to DNA-damaging agents. Thus, groups of fibroblast lines from patients with the motor neuron diseases spinal muscular atrophy and amyotrophic lateral sclerosis were not hypersensitive to a radiomimetic chemical,³⁹ while the groups of amyotrophic lateral sclerosis fibroblast²⁰ and lymphoblastoid (fig 2) lines studied had a normal sensitivity to ionizing radiation. These results with motor neuron disease lines do not rule out the possibility that an individual amyotrophic lateral sclerosis or spinal muscular atrophy line might be hypersensitive to these DNA-damaging agents^{24,39} or that motor neuron disease lines might be hypersensitive to some other type of DNA-damaging agent. However, spinal muscular atrophy and amyotrophic lateral sclerosis cells probably have no hypersensitivity to ultraviolet irradiation, since the patients' sun-exposed skin is not known to have clinical hypersensitivity to the ultraviolet irradiation in sunlight.

The specificity of the hypersensitivity of the radiosensitive neurodegenerations for the X-ray-type of DNA-damaging agent, as apposed to the ultraviolet irradiation type, has been well documented by the normal response to ultraviolet irradiation found in cultured cells from patients with ataxia telangiectasia,^{1,12,18} Huntington's disease,^{12,24} Parkinson's disease and Alzheimer's disease (*Results*). Thus, the radiosensitivity is not due to an inability to respond normally to all types of DNA-damaging agent. Specificity of the radiosensitivity as a feature of certain primary neuronal degenerations, as opposed to many other diseases affecting the nervous system, is attested to by the failure to find hypersensitivity to the lethal effects of the X-ray-type of DNA-damaging agent in cultured cells from patients with the following: (1) the demyelinating disorders multiple sclerosis⁴⁰ (fig 2) and Cockayne syndrome;^{12,13,18,31,40} (2) the primary neuronal degenerations xeroderma pigmentosum^{1,12,13,18,25} and motor neuron disease^{20,39} (fig 2); and (3) a group of 16 lymphoblastoid lines from patients with ten genetic disorders with neurological involvement but without primary degeneration of excitable tissue.¹² However, radiosensitivity has been found in cultured cells from patients with degeneration of certain nonneural excitable tissue, viz, skeletal muscle in the muscular dystrophies,⁴¹ including Duchenne muscular dystrophy,^{17,25} and photoreceptors in a primary pigmentary retinal degeneration, the autosomal recessive disorder Usher syndrome.¹⁷

The radiosensitivity in cultured nonneural cells from patients with Parkinson's disease and Alzheimer's disease is likely to result from a stable

genetic defect, as indicated by the maintenance of the radiosensitivity in the patients' serially propagated cells in tissue culture. We therefore postulate that the abnormality resulting in radiosensitivity of our sporadic Parkinson's disease and Alzheimer's disease patients' cell lines and in the premature death of their neurons *in vivo* is the result of a dominant somatic mutation occurring during embryogenesis and not involving the patients' germ cells. Involvement of the patients' germ cells would lead to a familial form of the disease. Lymphoblastoid lines from patients with Duchenne muscular dystrophy, a disease known to be either inherited or acquired by a spontaneous mutation,⁴² are also hypersensitive to X-rays.^{17,25}

Because the age of onset of neurodegeneration in xeroderma pigmentosum correlates with the degree of hypersensitivity *in vitro* of the patients' fibroblast and lymphoblastoid lines to killing by ultraviolet irradiation,^{1,4,6-8} the premature death of xeroderma pigmentosum neurons may result from the accumulation of unrepaired damage in neuronal DNA.^{1,2,4,6,7,9-11} Such damage would be caused by normally occurring DNA-damaging cellular metabolites, reactive oxygen species, and spontaneous hydrolytic reactions.^{1,43} Our DNA-damage hypothesis provides an explanation for the *in vitro* radiosensitivity and for the *in vivo* premature death of neurons in Parkinson's disease and Alzheimer's disease. Exposure of cells to X-rays *in vitro* results in many types of lesions in DNA. In normal cells a certain fraction of these potentially lethal lesions are unrepaired. In the Parkinson's disease and Alzheimer's disease patients' cells the fraction of these unrepaired lesions may be slightly higher due, perhaps, to the inability of the patients' cells to repair an infrequent type of normally repairable lesion. The resulting slight increase in number of lethal lesions remaining in the patients' cells could cause the hypersensitivity we have demonstrated. We postulate that there is defective repair of a type of potentially lethal lesion in the primary neuronal degenerations characterised by radiosensitivity. Since the DNA of neurons *in vivo* is constantly being damaged by spontaneous hydrolysis and intracellular metabolites,^{1,43} neuronal groups which undergo premature death would be those in which an unrepairable type of lesion represents a relatively large proportion of the potentially lethal lesions occurring. The different clinical and neuropathological patterns of these various disorders would result principally from different defective repair processes, from different mutations in the same repair process, or from different amounts of DNA damage. However, whatever the cause may be for the *in vitro* radiosensitivity we have described, the ability to

study such an abnormality in cultured nonneural cells from Parkinson's disease and Alzheimer's disease patients may make it possible to elucidate the underlying mechanisms responsible for these diseases.

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