RESPONSE

Dr. Stockmeier raised several important issues in the studies of neuropsychiatric illness with postmortem material. Most directly, he argued that changes reported in 5-HT_2 and 5-HT_{1A} receptors in schizophrenics may reflect an age effect rather than a disease effect (Joyce et al. 1993). I am addressing a number of points in rebuttal. First, the regions reported to be affected are more extensive than those described by Stockmeier in his letter. It was observed that there was an increased number of 5-HT_2 receptors in the ventral striatum, posterior cingulate, temporal cortex, and hippocampus of the schizophrenic as compared to the control group. There was also a marked elevation in the number of 5-HT uptake sites in the ventral striatum, and their striosome/matrix organization was modified. In contrast, there was a marked reduction in the number of sites in frontal cortex, anterior cingulate, and posterior cingulate. Increased numbers of 5-HT_{1A} receptors were found in the posterior cingulate, motor cortex, and hippocampus. However, as suggested by Stockmeier, reductions in the number of 5-HT_2 receptors in the prefrontal cortex of schizophrenics reported by other groups are likely to be real, and the issue was not adequately addressed in the study by Joyce and associates (1993). Decreased binding of [^{3}H]ketanserin and [^{3}H]spiperone to 5-HT_2 receptors in the prefrontal cortex (Brodmann's areas 9, 10) in schizophrenia have been reported in three studies (Mita et al. 1986; Arora and Meltzer 1991; Laruelle et al. 1993). The region analyzed in the study by Joyce and associates (1993), area 9 within the precentral gyrus, is not truly prefrontal cortex. The changes that were found in the prefrontal cortex in similar material suggest a regionally specific effect of 5-HT_2 receptor loss in the prefrontal cortex in schizophrenia (Laruelle et al. 1993).

Second, there are no effects of age on 5-HT_2 receptor numbers outside the prefrontal cortex. An age-effect on binding of [^{3}H]ketanserin or [^{3}H]spiperone to 5-HT_2 receptors in the prefrontal cortex of controls has been found (Marcusson et al. 1984; Cheetham et al. 1988; Gross-Isseroff et al. 1990; Laruelle et al. 1993); however, a lack of an age-effect for other regions of the cortex (temporal, occipital) and the hippocampus has also been demonstrated (Pazos et al. 1987b; Marcusson et al. 1984; Cheetham et al. 1988; Gross-Isseroff et al. 1990; Laruelle et al. 1993). No consistent age effects on 5-HT_{1A} receptor number have been reported. Binding of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors has been reported to show an age-dependent reduction in some regions of the male human brain, but no such age-dependent reduction was found in the female brain (Dillon et al. 1991). Other groups have reported no changes in 5-HT_{1A} receptor number with age (Pazos et al. 1987a), or only in the temporal cortex of cases over 60 years of age (Middlemiss et al. 1986). Nonetheless, age effects may contribute to our reported alterations in schizophrenic tissue, but our analysis of the data comparing the younger (31 $\pm$ 3.8 yrs, n = 4) to the older (61 $\pm$ 12 yrs, n = 6) age schizophrenic cases indicate otherwise. For example, [^{3}H]CN-IMI labeling of 5-HT uptake sites in Brodmann's area 9 was 152 $\pm$ 23 fmols/mg protein (mean $\pm$ SD) for the controls (68 $\pm$ 15 yrs, n = 8), 101 $\pm$ 13 fmols/mg protein for the total schizophrenic group, 94 $\pm$ 15 fmols/mg protein for the younger schizophrenic group, and 105 $\pm$ 13 fmols/mg protein for the older age schizophrenic group. Age effects are not found for changes in 5-HT uptake sites in the frontal cortex (Andersson et al. 1992), and consistent decreases in 5-HT uptake sites in prefrontal cortex of schizophrenics have been found (Joyce et al. 1993; Laruelle et al. 1993). The values for binding of [^{3}H]8-OH-DPAT to 5-HT_{1A} receptors and [^{125}I]LSD to 5-HT_2 receptors in different regions (no laminar analysis) are shown in Table 1. The data show that both the older age and the younger age groups of schizophrenics have similar qualitative changes in receptor number. This age-independent effect was also observed when beta-adrenergic receptor subtypes in human postmortem brains were analyzed for the same regions in schizophrenics and in controls (Joyce et al. 1992). This does not mean that there are no age-related changes in the control group, but that the alterations in the schizophrenic group are age-independent. These specific patterns of modified receptor number in schizophrenia may reflect neurodevelopmental alterations (Joyce 1993); thus, elevated numbers of 5-HT_{1A} and 5-HT_2 receptors in the hippocampus may reflect compensatory events to an insult to the 5-HT innervation to the cortex (Whitaker-Azmitia et al. 1990). The evidence for reduced 5-HT uptake sites, located on 5-HT terminals, in the prefrontal cortex along with reduced numbers of 5-HT_2 receptors may evidence an inability for compensatory events to occur in that region.

Third, I am not inferring that careful matching of controls and disease-related cases should not be undertaken. The results by Joyce and colleagues (1993) would be further strengthened by having included a younger

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Table 1. Regional Effects on Binding of [^{3}H]8-OH-DPAT to 5-HT$_{1A}$ Receptors and [^{125}I]LSD to 5-HT$_2$ Receptors in Age-Divided Schizophrenic Groups and the Control Groups

	5-HT$_{1A}$ Receptor by Region[b]				5-HT$_2$ Receptor by Region[b]			
	Schizophrenia			Control	Schizophrenia			Control
Region[a]	Group	Older	Young	Group	Group	Older	Young	Group
Area 9	112 ± 29	116 ± 21	108 ± 17	86 ± 14	23.2 ± 8	28.2 ± 6	19.3 ± 4	16.1 ± 3
Area 24	107 ± 33	114 ± 26	105 ± 23	87 ± 13	19.5 ± 7	23.4 ± 5	17.9 ± 4	16.8 ± 3
Area 23	131 ± 18	136 ± 9	124 ± 11	83 ± 18	21.4 ± 4	23.5 ± 3	20.3 ± 3	11.5 ± 2
Area 4	135 ± 14	138 ± 11	131 ± 12	64 ± 18	11.6 ± 4	10.2 ± 3	12.5 ± 3	8.6 ± 3
Area 1	133 ± 36	130 ± 31	141 ± 29	113 ± 9	8.9 ± 3	7.4 ± 3	9.3 ± 2	5.8 ± 2
Temporal	146 ± 27	140 ± 21	151 ± 19	134 ± 17	27.3 ± 5	21.5 ± 3	35.1 ± 3	16. ± 3
Ent Ctx	86 ± 18	89 ± 14	85 ± 11	76 ± 18	8.5 ± 3	8.8 ± 2	7.9 ± 2	7.4 ± 2
CA1	489 ± 34	513 ± 29	469 ± 25	377 ± 38	16.7 ± 3	15.1 ± 3	17.7 ± 3	10.1 ± 2
DG	344 ± 26	340 ± 18	354 ± 23	191 ± 29	13.2 ± 2	14.2 ± 3	12.5 ± 3	6.9 ± 2
Sub	254 ± 43	233 ± 35	267 ± 34	225 ± 35	4.4 ± 2	4.6 ± 3	4.1 ± 2	2.4 ± 2
Striatum	14 ± 4	16 ± 5	12.1 ± 2	15 ± 3	14.7 ± 3	11.9 ± 2	16.5 ± 3	8.1 ± 2

[a] Region, Area refers to Brodmann's areas of cortex.
[b] Units expressed as fmols/mg protein.

age, nonsuicide, control group; however, this would not have addressed the potential error of comparing young-age schizophrenics committing suicide with a young, nonsuicide control group. We made a comparison between the schizophrenic group (that included suicide and nonsuicide case) and a nonschizophrenic suicide group in a limited number of regions of the limbic cortex and the hippocampus. Alterations in these markers of the serotonergic system were different between groups. This supports that alterations of the 5-HT$_2$ and 5-HT$_{1A}$ receptors in the schizophrenic group were relevant to the psychopathology of this disease and not due to suicide (Arango et al. 1990). Arora and Meltzer (1991) also report the potential error associated with nonmatching between groups, in this case, of sex. The sex difference in numbers of 5-HT$_2$ receptors in the prefrontal cortex in the control group, with the females higher (n = 5,255 ± 66 fmols/mg protein) than the males (n = 6, 171 ± 39 fmols/mg protein), provides the sources of differences between the control group and the schizophrenic group (10 males, 1 female). The control female group is significantly higher in numbers of 5-HT$_2$ receptors than the schizophrenic males (F = 10.934, p = .0048); however, the control male group is not different from the schizophrenic males (F = 0.904, p = .3842). This points to the importance in matching control cases with schizophrenic cases on a number of characteristics. It should be possible to develop research programs incorporating acquisition of postmortem tissues that recognize the importance of matching control groups and disease groups by a number of criteria. This would include age, sex, postmortem interval, and race. It is also important to recognize that it will not be possible to match a number of other criteria that also appear important, including hospitalization period, drug history, and education level. A program for clinico-pathologic studies of schizophrenia has been introduced at the University of Pennsylvania that allows for antemortem assessment of drug history, diagnosis, hospitalization record, and neuropsychological testing (Arnold et al. 1994b), as well as postmortem assessment of possible accompanying neurodegenerative lesions (Arnold et al. 1994a); however, this does not address that different sites of research will have characteristics for their schizophrenic population that differ widely from other research sites. Hence, the comparison of results across research sites may continue to be limited.

The criticisms raised by Stockmeier do not diminish the relevance of the data published in *Neuropsychopharmacology* (8:315–336). They have, however, provided a useful forum for the discussion of a number of methodological issues that will be addressed in future studies.

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REFERENCES

Andersson A, Sundman I, Marcusson J (1992): Age stability of human brain 5-HT terminals studied with [^{3}H]paroxetine binding. Gerontology 38:127–132

Arango V, Ernsberger P, Marzuk PM, Chen J-S, Tierney H, Stanley M, Reis DJ, Mann JJ (1990): Autoradiographic demonstration of increased serotonin 5-HT$_2$ and β-adrenergic receptor binding sites in the brain of suicide victims. Arch Gen Psychiatry 47:1038–1047

Arnold SE, Franz BR, Trojanowski JQ (1994a): Elderly patients with schizophrenia exhibit infrequent neurodegenerative lesions. Neurobiol Aging (In Press)

Arnold SE, Gur RE, Shapiro, RM, Fisher KR, Moberg PJ, Gib-

ney MR, Blackwell P, Trojanowski JQ (1994b): Prospective clinico-pathologic studies of schizophrenia: accrual and assessment. Am J Psychiatry (In Review)

Arora RC, Meltzer HY (1991): Serotonin$_2$ (5-HT$_2$) receptor binding in the frontal cortex of schizophrenic patients. J Neural Transm [GenSect] 85:19–29

Cheetham SC, Crompton MR, Katona CLE, Horton RW (1988): Brain 5-HT$_2$ receptor binding sites in depressed suicide victims. Brain Res 443:272–280

Dillon KA, Gross-Isseroff R, Israeli M, Biegon A (1991): Autoradiographic analysis of serotonin 5-HT$_{1A}$ receptor binding in the human brain postmortem: Effects of age and alcohol. Brain Res 554:56–64

Gross-Isseroff R, Slama D, Israeli M, Biegon A (1990): Autoradiographic analysis of [^{3}H]ketanserin binding in the human brain postmortem: Effect of suicide. Brain Res 507:208–215

Joyce JN (1993): The dopamine hypothesis of schizophrenia: Limbic interactions with serotonin and norepinenphrine. Psychopharmacology 112:S16–S34

Joyce JN, Lexow, N, Kim SJ, Artymyshyn R, Cassanova M, Kleinman J, Bird E, Winokur A (1992): Distribution of Beta-adrenergic receptor subtypes in human postmortem brain: alterations in limbic regions of schizophrenics. Synapse 10:228–246

Joyce JN, Shane A, Lexow N, Winokur A, Casanova MF, Kleinman JE (1993): Serotonin uptake sites and serotonin receptors are altered in limbic system of schizophrenics. Neuropsychopharmacol 8:315–336.

Laruelle M, Abi-Dargham A, Casanova MF, Toti R, Weinberger DR, Kleinman JE (1993): Selective abnormalities of prefrontal serotonergic receptors in schizophrenia. Arch Gen Psychiatry 50:810–818

Marcusson JO, Morgan D, Winblad B, Finch CE (1984): Serotonin-2 binding sites in human frontal cortex and hippocampus. Selective loss of S-2A sites with age. Brain Res 311:51–56

Middlemiss DN, Plamer AM, Edel N, Bowen DM (1986): Binding of the novel serotonin agonist 8-hydroxy-2-(Di-n-Propylamino) tetralin in normal and Alzheimer brain. J Neurochem 46:993–996

Mita T, Hanada S, Nishino N, Kuno T, Nkai H, Yamadori T, Mizoi Y, Tanaka C (1986): Decreased serotonin S_2 and increased dopamine D_2 receptors in chronic schizophrenics. Biol Psychiatry 21:1407–1414

Pazos A, Probst A, Palacios JM (1987a): Serotonin receptors in the human brain-III: Autoradiographic mapping of serotonin-1 receptors. Neurosci 21:97–122

Pazos A, Probst A, Palacios JM (1987b): Serotonin receptors in the human brain-IV: Autoradiographic mapping of serotonin-2 receptors. Neurosci 21:123–139

Whitaker-Azmitia PM, Shemer AV, Caruso J, Molino L, Azmitia EC (1990): Role of high affinity serotonin receptors in neuronal growth. Ann NY Acad Sci 600:315–30