

Changes on Computed Cranial Tomography with Aging: Intracranial Fluid Volume

Leslie M. Zatz^{1,2}
 Terry L. Jernigan¹
 Albert J. Ahumada, Jr.³

A semiautomated computer analysis was developed to estimate fluid volumes in each hemicranium from computed tomography scans. The method was used to estimate total ventricular and sulcal fluid in 123 normal subjects aged 23–88 years. A wide range of normal values was found. The trend was for the estimated ventricular and sulcal fluid volumes to remain relatively constant until age 60 and then to increase at an increasing rate thereafter. Ventricular enlargement occurred in the absence of sulcal enlargement and vice versa. The estimate of the volume of the ventricles was related to skull size. When this was taken into account, the size of the ventricles showed no sex difference. The cranial cavity was larger in men than in women, and, in both genders, the left hemicranium and the left ventricle were larger on the average than their right counterparts. The limitations of computed cranial tomography as a quantitative tool are discussed in detail.

The ventricles, cisterns, and sulci of the brain are irregularly shaped. Enlargement of any of these areas alone or in combination may be significant in establishing the presence of a disease process. Thus, the measurement of the fluid volume in these spaces in normal subjects and in patients has been the goal of many investigators [1].

Early investigators with computed tomography (CT) used the techniques developed for pneumoencephalography to estimate fluid volumes. They made linear measurements of the size of the ventricles and derived combinations of these measurements or indices relating them to the diameter of the skull. Sulcal volume was estimated by measuring the maximum width of the largest sulcus or the sum of the width of the four largest sulci on sections above the level of the ventricles [2–6]. Recognizing the limitations of linear measurements to characterize an irregular volume, other investigators measured the ratio of the ventricular area to the area of the cranial cavity on one section, a ventricular-brain ratio (VBR) [7–9]. These are all indirect methods to measure the desired fluid volume and all suffer from the difficulty in accurately defining the borders of the ventricles and sulci on an image or numerical printout. Even if the borders could be accurately located, these methods can not take into account averaging of brain and cerebrospinal fluid (CSF) attenuation values within the thickness of the section.

With CT, data are available in digital form for analysis by computer. In a previous report [10], we described a semiautomated method to estimate total CSF volumes. We have modified the program to permit separate estimates of fluid volumes related to either the ventricles or the sulci [11]. We have used this method to study 123 normal volunteers, aged 23 to 88 years. Studies to validate the algorithm used in the analysis and the known sources of error in the method are presented in appendix A. To determine whether simple linear or area measurements can be used to estimate cranial fluid volumes, we examined the correlations between the automated measurements and several of these linear and area measurements of the intracranial fluid spaces (appendix B). In a

Received April 15, 1981; accepted after revision August 7, 1981.

This work was supported by Medical Research Service, Veterans Administration Medical Center, Palo Alto, CA.

¹ Radiology Service (114), Veterans Administration Medical Center, Palo Alto, CA 94304. Address reprint requests to L. M. Zatz.

² Department of Radiology, Stanford University School of Medicine, Stanford, CA 94305.

³ NASA/Ames Research Center, Mountain View, CA 94035.

AJNR 3:1–11, January/February 1982
 0195–6108/82/0301–0001 \$00.00

separate paper, we will report changes found in the white matter with age in the same subjects [12].

Subjects and Methods

Subjects

We scanned 123 normal volunteers between October 1977 and June 1980, 74 women and 49 men, whose informed consent to participate in the study was obtained after the nature of the study had been fully explained (table 1). Subjects, aged 23–65 years, were recruited from professional employees at the Palo Alto Veterans Administration Medical Center and from the community. They denied any history of physical or neurological problems. The subjects over 65 were participants in other projects on normal aging and had a screening history and physical examination. Studies on some of these subjects have been reported [13]. All volunteers considered themselves healthy for their ages and were active and independent. Subjects with a history of neurological problems other than occasional headaches or with major medical diseases (other than mild hypertension, whether or not treated with medication) were excluded. One subject who was over 65 was excluded from the study before data analysis because of the presence of a focal radiolucency on her CT scan consistent with a prior stroke.*

Computed Tomography Scans

All scans were obtained on a Syntex System 60 head scanner, a 180° translate-rotate scanner which obtains one complete scan in 1 min. The scans were made through a constant length plastic and water path at a plane of approximately 15° to the canthomeatal line. The CT value obtained for water is 0, and for air approximately –500 giving values similar in scale to the original EMI scanner. The abbreviation ES for EMI scale will be used to designate these values (on the Hounsfield scale the CT numbers would be about twice those on the EMI scale). The section thickness is 10 mm and the table is automatically moved 10 mm between each section. A pixel represents the average attenuation value of a volume 0.93 × 0.93 × 10 mm or 8.65 cubic mm. The Data General Eclipse S/200 minicomputer incorporated in the scanner was used to perform the analysis.

To relate comparable sections among subjects, a sequential numerical code was assigned to each section depending on the relationship of the sections to the bony and ventricular anatomy (fig. 1). Code 2 was the lowest analyzable section obtained just above the petrous pyramids and the orbital roofs. The ventricles were contained on sections coded 3–6, only extending into code 7 when very large. Sections coded 8 and 9 were above the ventricles and were the highest available in almost all subjects.

Computer Analysis

The ASI-II algorithm was modified to break each section into separate zones [10, 11]. For each section to be analyzed, the

TABLE 1: Age Distribution of Normal Subjects

Years	All	Males	Females
	No. (%)	No. (%)	No. (%)
20–29	11 (8.9)	6 (12.2)	5 (6.8)
30–39	11 (8.9)	6 (12.2)	5 (6.8)
40–49	21 (17.1)	9 (18.4)	12 (16.2)
50–59	16 (13.0)	12 (24.5)	4 (5.4)
60–69	22 (17.9)	9 (18.4)	13 (17.6)
70–79	36 (29.3)	7 (14.3)	29 (39.2)
80–89	6 (4.9)	0	6 (8.1)
Total	123	49	74

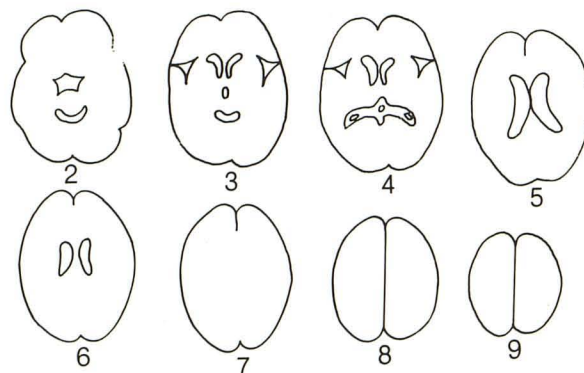


Fig. 1.—Schema for coding sections based on anatomy displayed in section.

following data were obtained at the viewing console and entered into the analysis: the coordinates for two or more points defining the midline; the center coordinates and diameters for one or more circular brain samples from each hemisphere; and the x,y coordinates defining the maximum length and width of the skull. The brain samples were taken from areas free of visible artifacts or CSF and which contained the largest proportion of white matter possible. They were taken as close to the center of the section as feasible to reduce bone-related spectral shift artifacts [14] while avoiding any fluid-containing structures on the sections above and below. The CT value for brain tissue used by the algorithm was the average CT value of the combined pixels in the squares circumscribed by the circular brain samples selected at the viewing console. It included a minimum of 98 pixels and was designated the healthy sample value (HS).

The model used to compute the CSF volume in each sample was first described by Walser and Ackerman [15]. It assumes that any sample contains only brain and/or CSF. The average CT value (D) of that sample is specified as follows:

$$D = P(f) D(f) + P(b) D(b), \quad (1)$$

where $P(f)$ and $P(b)$ are the proportions of CSF and brain respectively, and $D(f)$ and $D(b)$ are their characteristic CT values.

For the brain value, the mean CT value of the brain samples (HS) on each section was used. However, valid samples of CSF, which were not partial volume with brain, were not obtainable on every section. An assumption was made that the attenuation values for "normal brain" and for CSF would be relatively constant and that spectral shift artifacts [16] or linear drift [17] in CT values would affect both values equally. This seemed reasonable since there was no report of a change in the CT value of brain with atrophy or age before our study [12], and because normal variation in CSF com-

* After the study was completed, three additional subjects were found to have had medical conditions which would have excluded them from study. Two had suffered prior mild strokes, a woman, age 73, and a man, age 74. Another man, age 73, had undergone hormone therapy. The measurements for these subjects were not outliers on the scattergrams. Their z-scores for the fluid volume estimates were either within one SD of the mean or were less than the mean. If the latter, this indicated these individuals had less atrophy relative to their ages than did other subjects. In no case were their values such that exclusion would have affected the statistics or conclusions in a significant way. Thus, to avoid redoing the analyses, these subjects were not excluded.

position does not affect its CT value [18]. The difference between the CT value of brain and CSF, 13.0 ± 0.8 ES, was determined from CT scans of 20 subjects whose ventricles were large enough to permit sampling of intraventricular fluid without partial volume. The 20 subjects included two normal elderly, two patients with a question of occult low-pressure hydrocephalus, and 16 patients with moderate atrophy. Average age was 63. Once the difference between the CT values for brain and CSF was determined, the CSF value for any section was obtained by subtracting this difference from the HS value for that section.

The analysis first computed the HS value and variance. The program then scanned each hemicranium outward from the midline, until it reached the skull, forming adjacent four-pixel samples and comparing their means to HS. The criterion used for the skull was a sample, more than 20 pixels from the midline, which contained a pixel with a CT value of greater than 150 ES. Any sample within the skull in which the four pixels had a SD greater than 8 was excluded from analysis. A printout was obtained for every section studied which showed the distribution of the samples included in the analysis. The printouts were examined to be sure there was no aberration in the configuration of the samples. The total number of samples on a section, multiplied by four, gave the number of intracranial pixels. This was taken as the brain area or volume on that section and was used in the analyses as a measure of cranial size.

Substituting the observed sample value, $d(o)$, for D ; HS for $D(b)$; $HS - 13$ for $D(f)$; $1 - P(f)$ for $P(b)$; and solving for $P(f)$ yields an equation with which the fractional CSF volume in a sample can be obtained:

$$P(f) = [HS - d(o)] / 13. \quad (2)$$

Using equation 2, the program estimated the relative amount of fluid in each sample. These ranged from zero in pure "brain," i.e., samples whose CT value equalled HS, to one in pure CSF; samples with a CT value 13 ES below HS. Because of statistical variation in CT values both above and below this range, fluid proportion estimates less than zero and greater than one were obtained. In samples close to the skull, the spectral shift artifact elevated the mean CT value of brain above HS producing strongly negative fluid values. We elected to truncate all negative values at zero, hoping to obtain a more accurate fluid volume estimate. Unfortunately, this produced a slight overestimation of fluid values since random variation of brain values above the mean were ignored while those below the mean were interpreted as fluid. This overestimation was observable in the central zone but was obscured in the peripheral zone by a relatively larger underestimation of fluid caused by spectral shift artifact from the adjacent bone (see appendix A, phantom studies).

To obtain separate estimates of ventricular and sulcal volumes, each hemisphere on a section was divided into equal area medial and peripheral zones as follows: (1) the coordinates of the boundary between the two hemispheres were computed from the supplied midline coordinates; (2) the samples comprising the peripheral zones for each hemisphere were obtained by repeatedly peeling off and accumulating the outermost, previously unencountered, samples, one at a time from each horizontal line of the matrix proceeding from top to bottom; (3) the process of accumulating consecutive outer layers continued until samples were obtained, equal to half the total in the hemisphere; (4) the remaining hemisphere samples were considered medial samples (fig. 2).

Based on a preliminary analysis of the data from a subset of subjects (appendix A), we chose four of our automated measures to be used in the evaluation of global changes on our subject scans. These were:

1. *M3-7*. The total fluid pixels in the medial zones of sections code 3-7. This fluid volume correlated highly with measures of

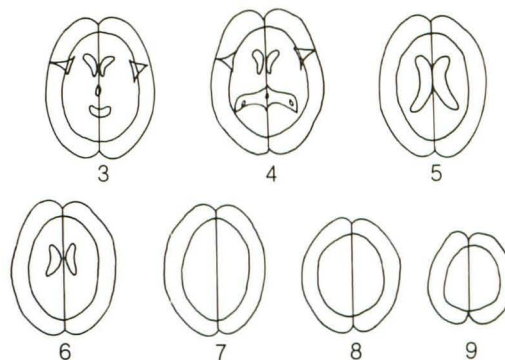


Fig. 2.—Schematic drawing of boundaries defined by program on each coded section.

ventricular size and was used as an estimate of the volume of the supratentorial ventricular system.

2. *P3-7*. The total fluid pixels in the peripheral zones of sections coded 3-7. This was an estimate of the volume of fluid in the temporo-Sylvian area and the cortical regions in the lower part of the supratentorial compartment.

3. *P8*. The number of fluid pixels in the peripheral zone of section code 8. This was an estimate of sulcal enlargement in the peripheral zone of a section above the ventricles.

4. *P9*. The number of fluid pixels in the peripheral zone of section code 9. This was an estimate of sulcal enlargement in the peripheral zone of the next higher section above the ventricles.

Statistical Methods

Multiple regression analyses were used to assess the separate and combined effects of age, cranial size, and gender on the fluid volumes. In these analyses, independent variables, for which the F to enter was significant at the 0.05 level, were only considered significantly related to the predicted measurement if the overall F for the regression also was significant (0.05 level). We included nonlinear transformations of certain variables in the regression analysis so that nonlinear effects, i.e., where a change in one of the variables accelerated over some range of values in the other variable, could be estimated and accounted for. Specifically, the square of cranial size (2d order polynomial) and both the square and cube (3d order polynomial) of age were entered as additional variables in the regressions whenever the size or age variable was entered. We indicate where this occurred and the degree of the polynomial used.

Results

Cranial Size and Symmetry

The cranial size (and, by inference, the cranial volume) was considered the number of pixels in the intracranial samples computed by the algorithm on the sections analyzed. The mean cranial volume summed over sections coded 2-9 was 34,141 pixels for men and 30,633 pixels for women (fig. 3). The difference between the two, 3,508 pixels, was statistically significant ($p < 0.001$).

The volume of the left hemicranium summed over sections coded 2-9 was larger than the right in 92% of the women and 88% of the men (fig. 4). The average difference between the volume of the two hemicrania, left minus right, was 383 pixels (SD = ± 382 , $p < 0.001$). The difference between men and women was not significant.

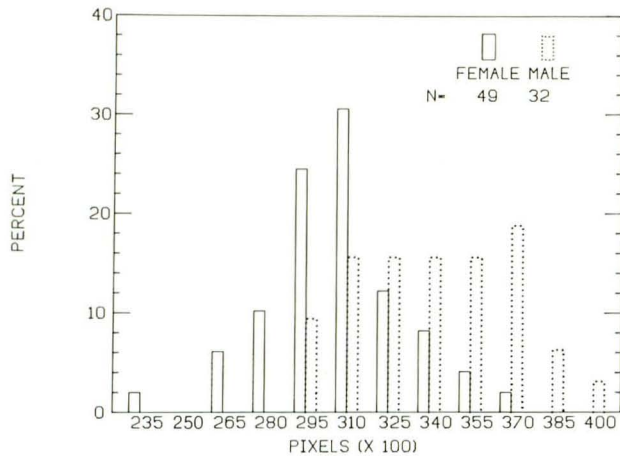


Fig. 3.—Distribution of cranial volume estimated by total pixels on sections coded 2–9. Subjects total less than 123 because not all had section code 9.

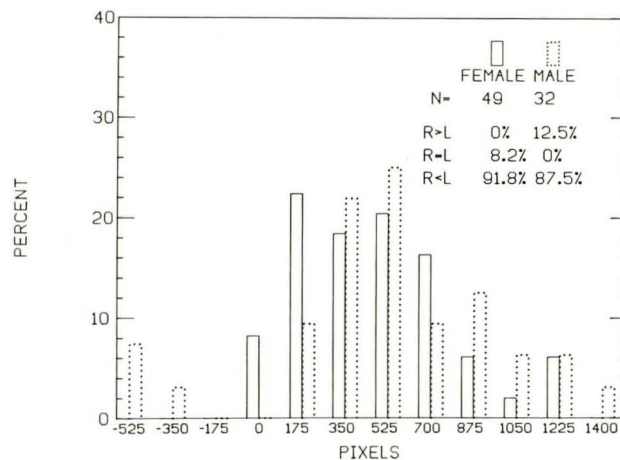


Fig. 4.—Cranial symmetry. Scale on abscissa is total pixels in left hemisphere minus total in right on sections coded 2–9. Subjects total less than 123 because not all had section code 9.

Using multiple regression analysis, no relationship was found between the volume of the intracranial compartment summed over sections 3–7 and age (3d order polynomial).

Ventricular and Sulcal Volume with Age

Multiple regression analysis was used to examine the relationships between our four automated measures and the size of the cranial cavity (2d order polynomial), age (3d order polynomial), gender, and the interactions between these variables. In each instance, the size of the cranial cavity was considered the number of intracranial pixels on the section(s) included in the automated measure. A few interactions between variables were significant, however, in every case they were explicable by weaknesses in the regression analysis or nonuniformity in the age distribution of the subjects, and did not appear to represent true interactions. After breaking out the effects of cranial size and age, gender played no significant role. Thus, hereafter, the data for men and women are not separated.

The size of the cranial cavity and its square accounted for 16% of the variance in M3–7 ($p < 0.001$), 7% of the variance in P3–7 ($p < 0.05$), and an insignificant amount of variance in P8 or P9. We use a suffix "C" to indicate that measures were "corrected" for the cranial size effect by subtracting from each subject's volume estimate the size and size squared terms derived from the multiple regression analysis.

The relationship between the various measures and age is shown in figures 5–8. The curves in the figures represent the best fitting polynomial on age, that is, the curve which best describes the change in the predicted means of the volumes with age. The statistical evaluation of the regressions of the measures on the third order polynomial for age is given in table 2 and the Pearson correlation coefficients for the relationships between the automated measures in table 3.

Ventricular symmetry was evaluated by subtracting right M3–7 from left M3–7 (fig. 9). The average difference was 48 pixels (SD = ± 86 , $p < 0.001$), indicating that, on the average, the left ventricle was larger than the right. The difference between men and women was not statistically significant.

Discussion

Previous investigators have attempted to measure changes in intracranial CSF volumes on CT scans indirectly by measuring the width of parts of the ventricles or by measuring the area of the ventricles on a single section. This study is, to our knowledge, the first report of changes in total intracranial fluid volumes with age in a large number of normal subjects. The computer algorithm includes an assumption of a constant difference between the CT values of normal brain and CSF which avoids the inaccuracies in other methods that utilize a fixed value or fixed range of values for CSF and/or brain. The model takes into account partial volume effects by assigning a proportion of fluid to each sample depending on the value of the CT number of the sample relative to the values for "pure" brain and "pure" CSF. Such partial volume effects may be more important in estimating the volume of normal relatively small ventricles and sulci, than in pathologically enlarged structures. The method is not fully automated and requires interaction with a human observer. A fully automated approach using pattern recognition techniques would be most desirable, however, such a method, avoiding the errors we discuss, has not been described or applied to a study of normal subjects.

Validation of the Algorithm

We attempted to validate the accuracy and reproducibility of the fluid volume measures, and their appropriateness as estimates of ventricular and sulcal volume in a number of ways (appendix A). Determination of the accuracy of the algorithm with a phantom was difficult because of physical problems in the *in vitro* methodology but the results appeared reasonable for clinical purposes (appendix A, D). Dual scans of patients and of a phantom showed the fluid

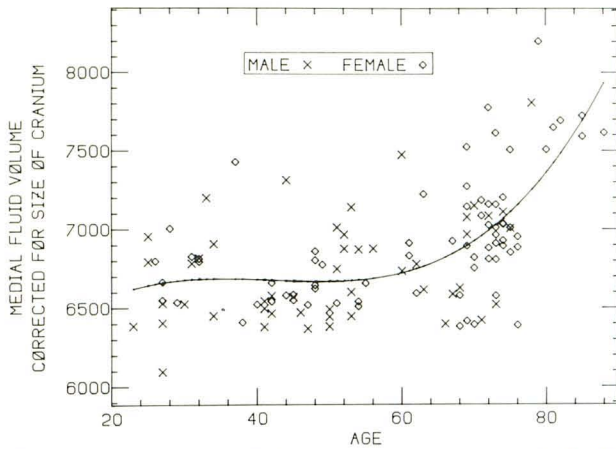


Fig. 5.—Corrected medial fluid volume, sections coded 3-7 (M3-7C), plotted against age. "Corrected" indicates relationship of cranial size has been removed from volume figure by subtracting 2d order polynomial. Volume is in arbitrary units. Curve represents relationship of corrected volume to 3d order polynomial on age with these terms: $M3-7C = 7.5(\text{age}) + .63(\text{age})^2 + .014(\text{age})^3 + 6694$.

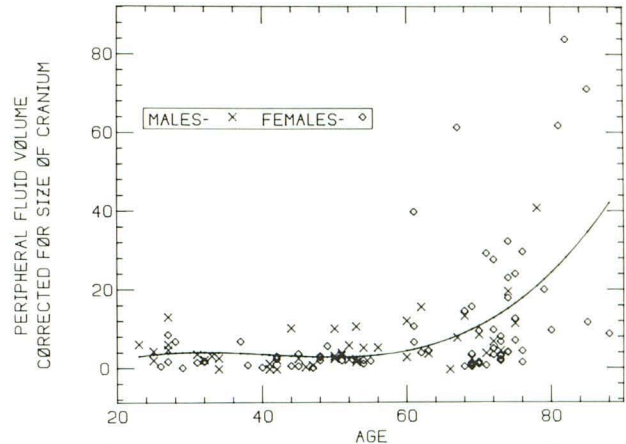


Fig. 7.—Corrected peripheral fluid volume, section code 8 (P8C), plotted against age. "Corrected" indicates relationship of cranial size has been removed from volume figure by subtracting 2d order polynomial. Volume is in arbitrary units. Curve represents relationship of corrected volume to 3d order polynomial on age with these terms: $P8C = .23(\text{age}) + .02(\text{age})^2 + .0004(\text{age})^3 + 3.51$.

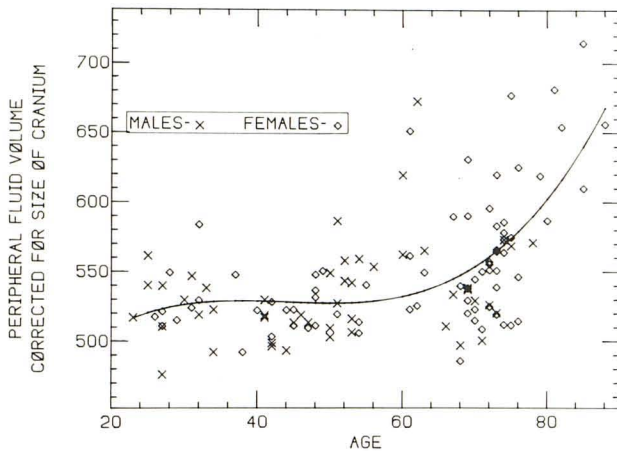


Fig. 6.—Corrected peripheral fluid volume, sections coded 3-7 (P3-7C), plotted against age. "Corrected" indicates relationship of cranial size has been removed from volume figure by subtracting 2d order polynomial. Volume is in arbitrary units. Curve represents relationship of corrected volume to 3d order polynomial on age with these terms: $P3-7C = .7(\text{age}) + .07(\text{age})^2 + .002(\text{age})^3 + 529$.

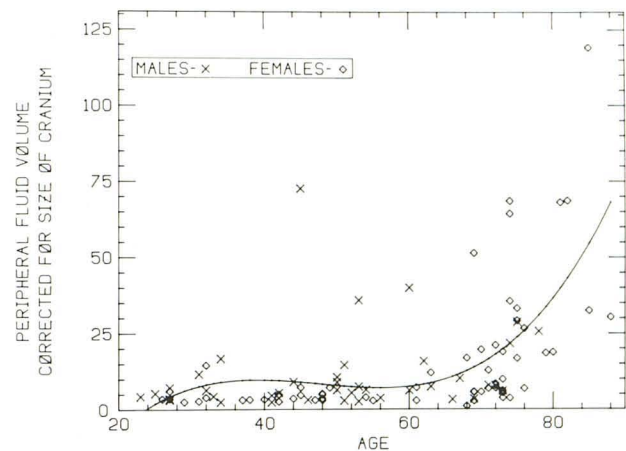


Fig. 8.—Corrected peripheral fluid volume, section code 9 (P9C), plotted against age. "Corrected" indicates relationship of cranial size has been removed from volume figure by subtracting 2d order polynomial. Volume is in arbitrary units. Curve represents relationship of corrected volume to 3d order polynomial on age with these terms: $P9C = .05(\text{age}) + .03(\text{age})^2 + .001(\text{age})^3 + 7.11$.

volumes to be reproducible despite changes in positioning (appendix A, E).

The estimate, M3-7, is not a direct measure of ventricular volume but an estimate of central fluid volume which includes in addition to the ventricles, parts of central cisterns and interhemispheric fissures. Its high correlation with an estimate of ventricular size in isolation (0.94) (appendix A, B) and with visual evaluations of size (table 4) permits its use as an estimate of ventricular volume (appendix A). The fact that it is not a measure of ventricular size in isolation may not be a deficiency. The attention to ventricular size in the past may have been one of convenience. That is, the ventricles are a well-defined structure large enough to be observed on radiographic studies or on brain specimens. As an indicator of central atrophy in the cerebrum of living subjects, our estimate of the volume of total fluid in the

TABLE 2: Multiple Regression Analyses of Major Variables on Age

Variable	Multiple R*	% Variance
M3-7C	0.63	40
P3-7C	0.60	36
P8C	0.53	28
P9C	0.59	35

Note.—Third order polynomial on age. For all statistics $p < 0.001$.

* "Multiple R" is a correlation coefficient that measures the association between the volume estimate and an optimal combination of the three age terms (3rd order polynomial). This takes values between 0 and 1 with the former indicating no relationship and the latter a perfect relation.

medial zones may be as, or more, valuable than the size of the ventricles alone.

Sulci can vary widely in size and a human observer's visual assessment may be influenced by factors that are not

TABLE 3: Correlations between Major Variables

	P3-7C	P8C	P9C
M3-7C	0.66	0.46	0.44
P3-7C	...	0.59	0.63
P8C	0.78

Note.—For all statistics $p < 0.001$.

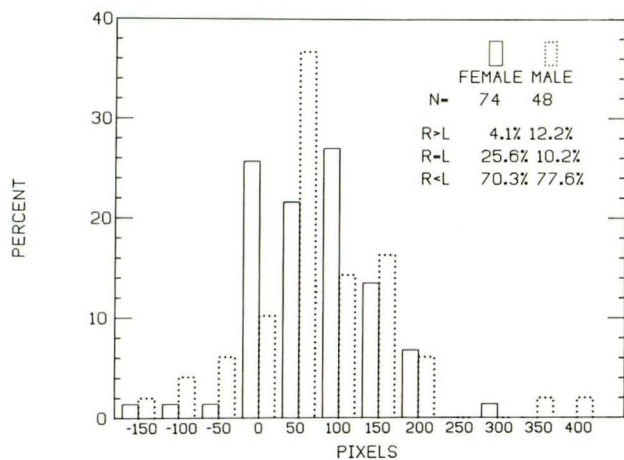


Fig. 9.—Ventricular symmetry. Scale on abscissa is total pixels in left M3-7 minus total in right.

obvious as indicated by the different relationship between the two visual evaluations, CRS1 and NYUS, and T8-9 (table 4) (see definition, appendix A). We concluded from the analyses of the visual evaluations that P8 and P9 were estimating vertex sulcal size, but that P3-7 was related to other fluid changes.

Cranial Size and Asymmetry

The volume of the cranial vault measured over sections coded 2-9 was significantly larger in men than women (fig. 3). The volume of the left hemicranium was larger than that of the right in 90% of our total group (fig. 4). Rotation of the head around a cranial-caudal axis would not affect the measurement of this asymmetry. Tilt of the head around a dorsoventral axis could alter this measurement if the direction and magnitude of the tilt were not randomly distributed. This factor was not assessed.

Previous reports indicated that, at autopsy, the brain of men on the average weighed slightly more than that of women [19]. The transverse diameter of the skull was found to be larger in men than in women in one CT study [3]; but in another no difference was found [20]. The statistical methods in the latter study were not described. There is conflicting evidence for a difference in weight between the two hemispheres [21]. Focal asymmetries in size of the two hemispheres are related to handedness and possibly language lateralization [22]. We did not have handedness data for all of our subjects. Alterations of normal patterns of cranial asymmetry have been reported in certain subgroups of schizophrenic patients [23].

TABLE 4: Correlations with Visual Evaluations

	CRV1	NYUV	CRS1	NYUS	CRTS
Ventricular measures:					
CRV1	0.85
CRV2	0.68
NYUV	0.84
M3-7	0.89	0.80
Sulcal measures:					
CRS1	0.81	...	0.34*
CRS2	0.93
NYUS	0.80
P3-7	0.45	0.34*	0.46
T8-9	0.80	0.65	0.31*
P8	0.87

Note.—CRV1 versus CRV1 and CRS1 versus CRS1 are correlations between evaluations made by rater 1 week apart.

* $p < 0.05$; for all other statistics, $p < 0.001$.

Ventricular Size and Asymmetry

The estimate of total fluid in M3-7, reflecting predominantly the ventricular volume, can be converted from pixels to milliliters, but there is little purpose in doing so. The sources of error in CT scanning are such that our estimates are not accurate measures of volume (appendix A). Because many of the errors in our method are generic to CT, this same caveat will apply to any quantitative analysis of CT scans. While these errors make the results inaccurate for absolute measurement of volume, the errors are not likely to affect comparisons between groups of subjects on the same scanner.

Our estimated ventricular volume was significantly related to skull size. When "corrected" for skull size, there was no difference due to gender. This has been suggested in prior literature. Gyldensted [3] found that the width of the anterior horns, the septum-caudate distance, and the minimum cella media distance were all positively related to the diameter of the skull. On the other hand, no difference due to gender was found for linear measures of ventricular size in two large CT series despite our finding that the cranium in men is larger than in women [20, 24]. The relation of our automated estimate of ventricular volume with age was improved by taking into account cranial volume. This is in the same direction as might occur with the use of a ratio of ventricular area to cranial area, which may, for the first time, provide experimental justification for the use of such a ratio [25].

The fluid volume of the left ventricle (as estimated by our technique) was larger than the right in 73% of our study population. Neither rotation nor tilt, as defined under cranial size, would affect the measurement of this asymmetry since the fluid volumes were summed over all sections in which the ventricles appeared. We did not have data on the handedness of all our normal subjects and thus did not analyze that relationship. The left ventricle has been noted to be larger in some dimensions than the right on pneumoencephalography [21]. Knudson (cited in [1]) found in his series of 183 brains that the left lateral ventricle was larger in 48%, the right was larger in 15%, and the two were equal in 37%. The evidence for an asymmetry on CT is based on linear measurements and is conflicting. Gyldensted [3] found that the left anterior horn width was greater than the right in

women while the left septum-caudate distance was greater than the right in men. Meese et al. [20] found no right-left asymmetry, however, their statistical methods were not described.

Fluid Volume Changes with Aging

Many studies of the effect of normal aging on CT scans are flawed by use of scans performed for clinical indications and interpreted as normal. In normal volunteer subjects, the increase in ventricular size with age until 60 is relatively slight but increases relatively rapidly thereafter. Sulcal width increases more consistently with age [3, 7, 20, 24, 26–29]. Sulcal and ventricular enlargement are weakly related [3, 7, 20, 28]. Recent studies show little evidence of atrophy below age 40 except in the frontal sulci [29], but much wider variation in the degree of atrophy in normal elderly subjects than did some of the earlier studies [26, 28]. Our results are consistent with these findings. Estimates of ventricular volume (M3–7C) and peripheral sulcal volume (P3–7C, P8C, and P9C) showed no significant upward trend until the seventh decade (figs. 5–8, table 2). Despite the relative homogeneity of our population, there was marked variation in the measurements on our older subjects and their range of values overlapped the range of fluid volumes of our subjects in their third decade. The correlations between the estimates of ventricular volume and the sulcal volumes on the higher sections were relatively weak, indicating that in some subjects ventricular and sulcal enlargement were not associated (table 3). There was a stronger relation between the estimate of ventricular volume and the estimate of combined sulcal and cisternal volume in the lower part of the cranial compartment, P3–7C.

Value of Linear and Area Measurements

The relation of several linear and area measurements to our computed estimates of ventricular and sulcal volume was examined (appendix B). The linear ventricular measurements all showed a positive correlation with the automated ventricular volume. The highest correlation was with the third ventricular width, 0.80. The next highest was with the summed septum-caudate distances, 0.67. Correlation of the anterior horn ratio or the cella media index with our corrected ventricular estimate, M3–7C, was weaker. As pointed out by Penn et al. [30], linear measurements are not directly proportional to volume and have serious deficiencies as indices of ventricular size. They can be used to follow changes in an individual patient's ventricular size if their limitations are kept in mind. They are inadequate for more sensitive quantitative studies.

We derived a computer ventricular-brain ratio (VBR) from the fluid volume in the medial zone of that section that had the greatest amount of fluid and the cranial size on that section (appendix B). Our computer derived VBR correlated highly with our estimate of total ventricular volume ($r = 0.90$, $p < 0.001$), confirming the findings of Penn et al. [30]. Our VBR measurement, however, was not the same as used by Penn et al. or by Jacobs et al. [27]. Neither of those groups of investigators used a model that accounted for

partial volumes. Both used fixed values for brain and CSF attenuation values. Penn et al. [30] were the only prior investigators who attempted to validate a VBR measurement as a criterion of ventricular volume. In the study by Jacobs et al. [27], planimetric and computer-derived VBR measurements were done on two different normal populations and compared. Direct comparison of the two techniques on the same scans was not made. As far as we are aware, a direct comparison between a planimetric and a computer-derived VBR has not been made. Since planimetric measurements are made visually on small CT images, when compared to computer methods they may have quite different systematic errors and may be susceptible to human biases. It cannot be assumed that our study or the two earlier ones have validated the planimetric method.

For many purposes, a visual rating of ventricular and sulcal size on a five step scale may be sufficiently accurate for clinical studies, particularly if a set of standard scans illustrating the steps is provided. Our clinical rating using that system gave a higher correlation with our ventricular estimate (0.89) and with our sulcal estimate, P8 (0.87), than did any of the linear measures. When such a visual rating system is used, however, it is difficult to establish that visual ratings of different structures present on the same section are independent.

Advantages of Computed Measurement Technique

The advantages of our technique include:

1. An estimate can be obtained of fluid volume in separate anatomic zones in each CT section. The fluid in these zones can be used to estimate the volume of the ventricles in each hemisphere and the volume of the sulci in different regions of the cranial cavity.
2. The program does not use an arbitrary CT value for brain or fluid. Spectral shift artifacts are reduced by obtaining these values from a sample of mixed brain on each section.
3. The program calculates the proportion of fluid in areas containing a mixture of fluid and brain (partial volumes).
4. Asymmetries in volume of the cranial vault and the ventricles around the midline can be measured.
5. The method can be adapted to other scanners to follow individual patients or to compare groups. However, brain-CSF difference and the criteria for recognizing the skull margins must be established for each machine. The results obtained on other scanners cannot be compared directly to those obtained in our normal volunteers because of the inaccuracies in CT scanning we have discussed. Patients must be compared to controls studied on the same scanner, under identical radiation conditions, and with monitoring, to be certain there is no change in the scanner over a period of time.
6. The method provides a means of estimating ventricular and sulcal size or cranial configuration which is blind to all clinical variables and to features of the scans themselves that might introduce bias into measurements made visually. This is important in studies in which differences are sought between diagnostic groups, in studies of cranial asymmetry,

or in studies in which the relationships between several CT variables are explored.

Conclusions

The estimated ventricular volume and three estimates of sulcal volume remain relatively constant from the early 20s to 60 years of age. After 60 the fluid volumes tend to increase but the range of normal values is wide.

The size of the ventricles is related to the size of the cranial vault. When corrected for cranial size, the ventricular volume in men and women does not differ.

The cranium is larger in men than in women. Regardless of gender, the left hemicranium is larger than the right in 90%, and the left ventricle is larger than the right in 73% of normal subjects.

Linear measurements of ventricular and sulcal size correlate with fluid volumes but are relatively poor measures. For many purposes, a visual rating of ventricular and sulcal size on a five step scale may be sufficiently accurate for clinical studies.

Our semiautomated CT analytic program can be used as a research tool to examine fluid content in the supratentorial compartment of the cranial cavity. The limitations of the method and of all quantitative studies with CT should be recognized. This program can be adapted to work on other scanners.

ACKNOWLEDGMENTS

Redmond P. Burke provided technical assistance and made constructive contributions to the study. Our collaborators provided subjects for our study as part of their own investigations. Forty-four normal elderly subjects were part of a study of aging conducted by Dr. Irwin Feinberg, M.D., Psychiatry Service, Veterans Administration Medical Center, San Francisco. James A. Moses, Ph.D., Psychology Service, and Bert Kopell, M.D., Adolf Pfefferbaum, M.D., Walton T. Roth, M.D., and Judith M. Ford, Ph.D., of the Psychiatry Service at the VAMC, Palo Alto, California, provided many of the subjects as part of their studies of aging, alcoholism, and schizophrenia.

Robert W. Jahnke, M.D., now at Lovelace Clinic, Albuquerque, New Mexico, assisted in the visual rating of the CT scans. M. J. DeLeon, Ph.D., New York University, supplied his group's clinical rankings of ventricular and sulcal enlargement on the scans of our subjects.

Appendix A: Validation of the Analytic Algorithm

A. Nomenclature

These abbreviations are used:

CRSn	visual rating of sulcal enlargement by rater n
CRTS	visual rating of temporo-Sylvian sulcal and cistern enlargement by rater one
CRVn	visual rating of ventricular enlargement by rater n
NYUS	visual rank ordering for sulcal enlargement by New York University group
NYUV	visual rank ordering for ventricular enlargement by New York University group
Ma-b	number of fluid pixels in medial zone on sections coded a-b from computer analysis

Pa-b	same as Ma-b but for peripheral zone
Ta-b	same as Ma-b but for the combined medial and peripheral areas of sections indicated
HSa	mean CT value of total mixed brain samples (healthy sample) on a section
r(p)	Pearson product moment correlation coefficient with the probability of a chance occurrence in parentheses.

B. Anatomical Relation of Ventricles to Zones

Visual inspection of the printouts of the ASI-II program and a detailed anatomic study of four subjects with a wide range of ventricular sizes [31] showed that the ventricles were consistently within the medial zones on codes 3-7 (M3-7). M3-7 also includes fluid-filled structures other than the ventricles. To determine how these extraventricular fluid volumes influenced the use of M3-7 as an estimate of ventricular volume, coordinates were obtained in 30 subjects that isolated the ventricles from other fluid-containing areas, and the ventricular size was measured with a program described previously [10]. The correlation of this measure with the automated estimate, M3-7, was 0.94 ($p < 0.001$) indicating that the validity of the M3-7 measure as an estimate of ventricular volume was not affected by the inclusion of extraventricular fluid in areas that were within the medial zone of the sections.

C. Visual

Using a subset of 44 normal subjects, two neuroradiologists visually rated the set of sections for each subject for ventricular enlargement, sulcal enlargement, and enlargement of the temporo-Sylvian sulci and cisterns on a five step scale. The ratings were done independently and one radiologist repeated the ratings 1 week later to measure intraobserver variation. These same scans were sent to a group of investigators at New York University (NYU) where they were visually rank ordered for ventricular size and sulcal enlargement by their technique [32] (table 4). The intergroup correlation is of the same order of magnitude as our inter- and intrarater correlations suggesting that all observers were evaluating the same structures. Comparison of the automated estimate of ventricular volume, M3-7, with the visual evaluations indicated that M3-7 reliably estimated what observers considered to be ventricular size and could be used as an estimate of ventricular volume (table 4).

A similar approach was used to evaluate our automated measurements of sulcal volume (table 4). The relationships were different for measures in the lower sections (CRTS, P3-7) than for those in the higher sections (CRS, NYUS, T8-9). Since atrophy in the vertex area might have different neurologic import than atrophy in the temporo-Sylvian and frontal pole regions, P3-7 was analyzed separately.

On the high sections, codes 8 and 9, the spectral shift artifact from bone was prominent in the peripheral zones. The separate contributions of the medial and peripheral zones to the relationship with the clinical rating on section code 8 were analyzed. The fluid volume on the section was visually rated in total and then, at a second sitting, with the medial zone blocked out. The visual rating of the peripheral zone correlated well with the automated estimate in the peripheral zone ($r = 0.84$). The visual rating of the total section correlated better with the automated peripheral estimate ($r = 0.87$) than with either the automated medial estimate ($r = 0.60$) or the automated estimate of fluid on the entire section ($r = 0.62$). These correlations suggested that the visual ratings were strongly related to the automated peripheral fluid estimate and that the addition of the medial fluid measure weakened the correlation.

The stronger relationship of the peripheral fluid with the visual evaluation than the medial fluid was caused by technical factors. Because the spectral shift artifact generally elevated the CT values close to bone, the peripheral fluid measure missed sulci in this area, but, concomitantly, there were few brain values lower than the HS mean and misinterpreted as fluid. Sulci in the peripheral zone were not measured totally by this technique but appeared to be sampled accurately because they were distributed diffusely. In the medial area, where the CT values were less affected by the spectral shift artifact, random variation of the CT values below HS was computed as fluid; random variation of CT values above HS, which computed as negative fluid volumes, was truncated by the computer program. This produced an overestimation of fluid in this area (see computer analysis, Methods, and sections D and F following). We used only the automated measures for the peripheral zones on sections code 8 and 9 in this report.

D. Phantom Studies

In an attempt to determine the accuracy of the ASI-II program, a phantom was constructed from a human skull, Rexolite (a polystyrene copolymer) "ventricles" and "sulci", and a glucose solution to mimic brain tissue. The complete phantom was scanned twice at different angles to determine the reproducibility of the computed measures (see next section for results). It was then scanned separately for "sulcal" volume and "ventricular" volume with only those components in place. Values for "brain" were measured in the medial zone without the ventricular model in place.

The volumes of the models of the ventricles and sulci were measured by water displacement and compared to that computed by our standard automated program. A second computation was made without the truncation of negative fluid values described under Methods, Computer Analysis, in the main text (table 5). The volume of the "sulci" were slightly underestimated, which is not surprising since the spectral shift artifact obscured sulci close to bone. The overestimation of the "ventricular" volume may have been the result of several errors. It was the same order of magnitude as the overestimation in "brain, medial" where there was no fluid. The difference between the computed and the measured value for "ventricles" was reduced when the truncation for brain values below zero fluid was removed, but the volume was then underestimated. This underestimation was the same order of magnitude as the negative error for "brain, medial" not truncated, the latter probably reflecting spectral shift artifact in the periphery of the medial zone. This artifact would have spuriously raised some CT values above HS. Those values would then have been computed as less than zero fluid. Such an effect would be even greater in the peripheral zones, which was the reason we chose to truncate the values at zero fluid. Another source of error in these phantom studies was our lack of control over the temperature of the fluid both in the phantom and in the water bag [33].

E. Reproducibility

The percentage difference between values obtained for the scans of the phantom at two different scan angles were: "ventricular" volume 10%; "sulcal" volume 12%; and total "fluid" volume 8%. Eleven cooperative patients who were having scans for clinical indications were scanned twice. These patients were not included in our normal series. For the second scan the patient's head was repositioned at a different angle to the scanning plane than was used for the first scan (table 6). The reproducibility is acceptable for comparing scans in a longitudinal study of patients.

TABLE 5: Results of Phantom Study

	Measured	Computed Standard	Computed Not Truncated
"Sulci"	21	18	...
"Ventricles"	46	61	40
"Brain, Medial"	0	13	-7

Note.—All measurements are in milliliters.

TABLE 6: Comparison of Dual Patient CT Scans

	No.	Difference (%)	Correlation Coefficient
		Mean ± SD	
M3-7	8	8 ± 6	0.80 ($p = 0.003$)
P3-7	8	13 ± 23	0.62 ($p = 0.036$)
P8-9	11	9 ± 21	
P8	11	...	0.90 ($p < 0.001$)
P9	11	...	0.98 ($p < 0.001$)

F. Sources of Error

Quantitative analysis of CT scans has serious limitations. These arise from inherent inaccuracies in computed tomography which include x-ray beam energy changes, artifacts from sampling, and drift in the detectors and electrical systems [14, 17]. While the x-ray attenuation coefficients of brain and CSF may be reasonably constant, the CT numbers obtained on scanning will vary depending on the geometry of the scanner, the generator settings, the reconstruction algorithm, the size and shape of the head, the thickness of the bone, and the presence and nature of any packing material used around the head. These variations will occur on the same scanner from section to section, as well as from scanner to scanner. A model to compensate for linear drift in CT values, recently described [17], is not applicable to the determination of fluid volumes.

The known sources of error in our method are:

1. The assumption that the difference between the CT value of brain and CSF on each section is constant may be incorrect. The decrease of HS with age, an unexpected finding in our study, revealed a potential error in our results [12]. Due to this decrease our algorithm would have underestimated the increase in fluid volume with increasing age. This was because our brain-CSF difference was derived from subjects whose average age was 63 leading to an overestimation of fluid volumes in our younger subjects. From the regression of HS on age [12], the mean HS value would be predicted to decrease by 2.6 ES between age 20 and 80. This is a 20% change in the assumed brain-CSF difference and could result in errors in fluid volumes of up to that order of magnitude over our age range. It seems unlikely that an error of that size would change any of our results or conclusions.
2. The analysis is very sensitive to the CT value of the brain samples (HS). The proportion of white and gray matter in the samples varied from section to section. If the HS value is raised by the presence of gray matter, whose CT value is 2-3 ES higher than white matter, then white matter will be interpreted as partial volume fluid by the algorithm resulting in an overestimation of fluid. If the HS value is lowered by the inclusion of partial volume CSF in the samples, then the actual amount of fluid will be underestimated by the algorithm. The determination of the value of white matter with a three compartment model, further subdividing brain into gray and white matter, rather than our two compartment model, e.g., brain and CSF, might decrease this error [34]. We are not sure whether

implementation of such a model is possible. We believe that visual selection of the brain samples by a trained observer is currently more reliable than any available automated algorithm.

3. Fluid volume was overestimated in the medial zones of the sections because of truncation errors. The use of a scanner with higher precision than ours would reduce the magnitude of this error. We truncated all fluid values below zero to zero so we could obtain volume measures to compare with values reported in the literature. If a statistic other than fluid volume is used, negative values could be tolerated for comparisons and truncation could be eliminated.

4. The amount of fluid adjacent to bone was underestimated because of the increase in CT value in this area produced by spectral shift artifacts. This artifact has been reduced but not eliminated in other commercially available scanners.

5. The implicit assumptions that the head was moved exactly 10 mm for each scan and that the sensitivity profile of the scan across the thickness of the section was uniform were not met [35].

Appendix B: Value of Linear and Area Measurements

A. Linear Measurements

On a subset of 42 subjects, linear measurements were made which included the maximum width of the four largest sulci on the sections above the ventricles, the width of the cella media (the minimum width of the bodies of both lateral ventricles at the narrowest point in their midportion), the greatest width of each anterior horn, the septum-caudate distances for each ventricle, the widest internal diameter of the skull on the section used for the ventricular measurements, and the width of the third ventricle at its widest point [3]. From these linear measurements, an anterior horn ratio (the maximum width of the anterior horns divided by the widest diameter of the skull on that section) similar to Evan's ratio, and the cella media index (the widest diameter of the skull divided by the cella media width) were calculated [3]. These measurements were made from the x,y coordinates of a movable cursor which were displayed on the viewing console.

For a description of the nomenclature of the automated measures, see appendix A, section A. The correlations between the linear measures and our estimate of ventricular volume, M3-7, were ($p < 0.001$ for all): minimum width, cella media, 0.59; summed width, anterior horns, 0.60; summed septum-caudate distances, 0.67; and width, third ventricle, 0.80.

The correlations between the ratios involving skull size and our estimate of ventricular size corrected for skull size, M3-7C, were: cella media index, -0.51 ($p < 0.001$); anterior horn ratio, 0.39 ($p = 0.008$).

The correlation between the two linear measurements of sulcal enlargement and our automated volume estimates were: P3-7, 0.26 ($p = 0.056$) for the maximum sulcus and 0.38 ($p = 0.009$) for the sulci sum; for P8-9, the maximum sulcus was 0.39 ($p = 0.021$) and the sulci sum was 0.60 ($p < 0.001$).

B. Area Measurements

For each normal subject, we computed a ventricular-brain ratio (VBR) with our program on the section for which the ventricular estimate was largest and compared it to our estimate of the total ventricular volume of the same individual. The automated measurement of the fluid in the medial zone on that section was taken as the automated ventricular area; the total number of pixels on the section was taken as the brain area; and the ratio of the two as the automated ventricular-brain ratio. The correlations were: automated ventricular area versus M3-7, 0.96 ($p < 0.001$); automated ventricular-brain ratio versus M3-7C, 0.90 ($p < 0.001$).

REFERENCES

1. Bull JWD. The volume of the cerebral ventricles. *Neurology* **1961**;11:1-9
2. Banna M. The ventriculo-cephalic ratio on computed tomography. *J Can Assoc Radiol* **1977**;28:205-210
3. Gyldensted C. Measurements of the normal ventricular system and hemispheric sulci of 100 adults with computed tomography. *Neuroradiology* **1977**;14:183-192
4. Hahn FJY, Rim K. Frontal ventricular dimensions on normal computed tomography. *AJR* **1976**;126:593-596
5. Haug G. Age and sex dependence of the size of normal ventricles on computed tomography. *Neuroradiology* **1977**;14:201-204
6. Huckman MS, Fox J, Topel J. The validity of criteria for the evaluation of cerebral atrophy by computed tomography. *Radiology* **1975**;116:85-92
7. Barron SA, Jacobs L, Kinkel WR. Changes in size of normal lateral ventricles during aging determined by computerized tomography. *Neurology* **1976**;26:1011-1013
8. Roberts MA, Caird FI, Grossart KW, Steven JL. Computerized tomography in the diagnosis of cerebral atrophy. *J Neurol Neurosurg Psychiatry* **1976**;39:909-915
9. Synek V, Reuben JR. The ventricular brain ratio using planimetric measurement of EMI scans. *Br J Radiol* **1976**;49:233-237
10. Jernigan TL, Zatz LM, Naeser MA. Semiautomated methods for quantitating CSF volume on cranial computed tomography. *Radiology* **1979**;132:463-466
11. Jernigan TL, Zatz LM, Feinberg I, Fein G. The measurement of cerebral atrophy in the aged by computed tomography. In: Poon LW, ed. *Aging in the 1980's, psychological issues*. Washington DC: American Psychological Association, **1980**: 86-94
12. Zatz LM, Jernigan TL, Ahumada AJ Jr. Changes on computed cranial tomography in white matter with aging. *J Comput Assist Tomogr* **1981**, in press
13. Feinberg I, Fein G, Price LJ, Jernigan TL, Floyd TC. Methodological and conceptual issues in the study of brain-behavior relations in the elderly. In: Poon LW, ed. *Aging in the 1980's, psychological issues*. Washington DC: American Psychological Association, **1980**:71-77
14. Zatz LM, Alvarez RE. An inaccuracy in computed tomography: the energy dependence of CT values. *Radiology* **1977**;124:91-97
15. Walsler RL, Ackerman LV. Determination of volume from computerized tomograms: finding the volume of fluid-filled brain cavities. *J Comput Assist Tomogr* **1977**;1:117-130
16. DiChiro G, Brooks RA, Dubal L, Chew E. The apical artifact: elevated attenuation values toward the apex of the skull. *J Comput Assist Tomogr* **1978**;2:65-70
17. Thaler HT, Rottenberg DA, Pentlow KS, Allen JC. A method of correcting for linear drift in computed tomography brain scans. *J Comput Assist Tomogr* **1979**;3:252-255
18. Hatam A, Berggren BM, Bergstrom M, Hindmarsh T. Attenuation values of the cerebrospinal fluid (CSF). *Neuroradiology* **1978**;15:165-166
19. Cobb S. Brain size. *Arch Neurol* **1965**;12:555-561
20. Meese W, Kluge W, Grumme T, Hopfenmuller W. CT evaluation of the CSF spaces of healthy persons. *Neuroradiology* **1980**;19:131-136
21. LeMay M. Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann NY Acad Sci* **1976**;280:349-366
22. Galaburda AM, LeMay M, Kemper TL, Geschwind N. Right-left asymmetries in the brain. *Science* **1978**;199:852-856
23. Luchins DJ, Weinberger DR, Wyatt RJ. Schizophrenia, evi-

- dence of a subgroup with reversed cerebral asymmetry. *Arch Gen Psychiatry* **1979**;36:1309-1311
24. Gonzalez CF, Lantieri RL, Nathan RJ. The CT scan appearance of the brain in the normal elderly population: a correlative study. *Neuroradiology* **1978**;16:120-122
 25. Zatz LM. The Evan's ratio for ventricular size: a calculation error. *Neuroradiology* **1979**;18:81
 26. Earnest MP, Heaton RK, Wilkinson WE, Manke WF. Cortical atrophy, ventricular enlargement and intellectual impairment in the aged. *Neurology* **1979**;29:1138-1143
 27. Jacobs L, Kinkel WR, Painter F, Murawski J, Heffner RR Jr. Computerized tomography in dementia with special reference to changes in size of normal ventricles during aging and normal pressure hydrocephalus. In: Katzman R, Terry RD, Bick KL, eds. *Alzheimer's disease: senile dementia and related disorders*. New York: Raven, **1978**:241-260
 28. Jacoby RJ, Levy R, Dawson, JM. Computed tomography in the elderly: 1. the normal population. *Br J Psychiatry* **1980**;136:249-255
 29. Cala LA, Thickbroom GW, Black JL, Collins DWK, Mastaglia FL. Brain density and cerebrospinal fluid space size: CT of normal volunteers. *AJNR* **1981**;2:41-47
 30. Penn RD, Belanger MG, Yasnoff WA. Ventricular volume in man computed from CAT scans. *Ann Neurol* **1978**;3:216-223
 31. Burke RP. Applications of cranial computed tomography: establishing an anatomical basis for the ASI-II subsegmentation program. Thesis submitted in partial fulfillment of requirements for honors in Human Biology, Stanford University, March 17, **1980**
 32. De Leon MJ, Ferris SH, George AE, et al. Computed tomography evaluations of brain-behavior relationships in senile dementia of the Alzheimer's type. *Neurobiol Aging* **1980**;1:69-79
 33. Bydder GM, Kreef L. The temperature dependence of computed tomography attenuation values. *J Comput Assist Tomogr* **1979**;3:506-510
 34. Thaler HT, Ferber PW, Rottenberg DA. A statistical method for determining the proportions of gray matter, white matter, and CSF using computed tomography. *Neuroradiology* **1978**;16:133-135
 35. Brooks RA, DiChiro G. Slice geometry in computer assisted tomography. *J Comput Assist Tomogr* **1977**;1:191-199