Hypertensive disease and cerebral oedema¹

MASAZUMI ADACHI, WILLIAM I. ROSENBLUM, AND IRWIN FEIGIN

From the Departments of Pathology, New York University Medical Center, Bellevue Hospital, and the Isaac Albert Research Institute, New York, U.S.A.

Previous studies have demonstrated the presence in the brains of some hypertensive individuals of pathological changes characteristic of the late effects of cerebral oedema (Feigin and Popoff, 1963; Feigin, 1966). These consist of a degeneration of the deeper white matter with a relative preservation of the arcuate zone and of the overlying cortex. The degenerated tissues are softened, retracted, slightly gray in colour, and may be partially destroyed and even cystic. Microscopically, the affected tissues are pale with most stains. A few hypertrophied astrocytes may be seen with ordinary stains, but with gold sublimate impregnations, the great majority of astrocytes appear poorly stained, small and distorted in shape, with processes which are shortened, thickened, poorly formed, and decreased in number. The number of myelinated fibres is decreased, at times markedly so, and rarely, the loss is complete. An axon loss of lesser severity is evident. The walls of the smaller blood vessels are often thickened and hyalinized. The myelin and astrocytes of the arcuate zone are often sharply distinguished from those in the deeper white matter by their normal appearance and number.

The localization of the changes is like that of acute oedema, and the astrocytic changes appear to represent a persistence and extension of those seen in acute oedema (Greenfield, 1939; Feigin and Popoff, 1962). In the acute stages, the astrocyte cell bodies may be well stained, at times somewhat enlarged and rounded; the processes may be fragmented though well stained, or short, stubby, variably stained, and decreased in number. The myelin loss is not evident in the acute stage, in which a separation of myelinated fibres showing only modest intrinsic changes, is noted. More severe myelin changes, including evidence of destruction and phagocyte formation, is evident in the subacute stages (Jellinger, 1966).

It was concluded that hypertensive individuals

differ from normotensive in having a much greater tendency to develop cerebral oedema following obvious local brain injury, such as infarcts or haemorrhages, or less obvious, more diffuse injury such as is seen in Binswanger's encephalopathy (Feigin and Popoff, 1963). This inference was drawn in a study of cases selected because of the presence of lesions characteristic of oedema, these forming a small minority of the total cases of hypertensive disease. The present study concerns the majority of hypertensive individuals, those with no grossly evident abnormality in the tissues. It would appear that stigmata of antecedent or continuing oedema are present in these as well.

MATERIALS AND METHODS OF STUDY

A series of human brains from hypertensive individuals was fixed in 20% formalin-1% acetic acid for one to two weeks. Immediately after coronal section, specimens of apparently normal tissues were weighed, then dried to constant weight at 67°C. or 56°C., this taking up to 144 hours. The decrement in weight, expressed in relation to the original weight of the sample, was considered to represent readily volatile water. The water analyses were performed by two separate investigators, using material from three different hospitals. One investigator (M.A.) analysed duplicate samples of cortex, arcuate white matter, deep white matter, and corpus callosum. One specimen from each of four tissues was taken before the second specimens were obtained. The other investigator (W.R.) examined single samples from the deep white matter only.

Tissues adjacent to those studied for water content were embedded in paraffin for histological study. These sections were stained routinely with haematoxylin and eosin, the Luxol blue-periodic-acid-Schiff stain, a gold sublimate technique (Naoumenko and Feigin, 1961), and occasionally by other stains.

Twenty-nine unselected hypertensive cases were chosen originally, from which 12 were segregated for this study. The other 17 were all cases in which evidence of congestive right heart failure was present, either at necropsy or in clinical descriptions shortly before death. In the cases with congestive failure, the water content of the white matter was significantly higher than in the 12 hypertensive cases being reported in which no congestive failure was present, raising the possibility that congestive failure in

¹This study was supported in part by research grant HE 02872 of the National Heart Institute of the United States Public Health Service, and forms part of a study of cerebral vascular diseases at Bellevue Hospital by the Cornell-New York University Study Group on cerebral vascular diseases.

itself may produce cerebral oedema. Since it was our specific aim to study the effects of hypertensive disease, it was thought wise to exclude the 17 cases in failure from this investigation.

The cases being reported all had documented blood pressure readings above 160 systolic and 100 diastolic except for three. Case 1 had a maximal recorded pressure of 180/80 mm.Hg., but there was a history of hypertension for 10 years, the heart was hypertrophied (420 g.), and the kidneys revealed arteriolar nephrosclerosis. Case 8 had a maximal recorded pressure of 200/90 mm.Hg. The heart weighed 480 g., and the kidneys revealed Kimelstiehl-Wilson lesions. Case 12 had a maximal recorded pressure of 180/90 mm.Hg. There was a clinical history of hypertension, for which medication had been given; the heart weighed 460 g. and the kidney revealed arteriolar nephrosclerosis. All of the cases fulfil the criteria for hypertension adopted jointly by the American Heart Association and the National Heart Institute, *i.e.*, systolic above 160 or diastolic above 95 (Doyle, 1960). The pathological changes in heart and kidney in cases 1, 8, and 12 lead us to believe that a more complete clinical documentation would have disclosed higher blood pressure readings than those noted.

A clinical diagnosis of 'malignant' or 'accelerated' hypertension was made in cases 9 and 10, but characteristic necrotizing vascular lesions in kidney and viscera were present at necropsy only in the former. 'Hypertensive encephalopathy' was not diagnosed in any of the cases. The kidney revealed lesions of chronic glomerulonephritis in cases 10 and 11. All of the other cases are best characterized as benign essential hypertension, and all revealed arteriolar changes in the kidney. Two of the cases (cases 7 and 10) showed hypertensive fibrinoid arteritis in the brain, a change which was not accompanied by, and is unrelated to, fibrinoid arterial lesions in other organs (Feigin and Prose, 1959).

OBSERVATIONS AND RESULTS

The data for the water content of the brain tissues are summarized in Table I, which includes in addition, the mean values for the brains of normal individuals studied earlier (Adachi and Feigin, 1966). The water content of the cortex is essentially identical to that in the normal cortex, and is like that reported for fresh unfixed normal brain (Folch-Pi and LeBaron, 1957). The water content of the arcuate white matter is essentially the same as that in this tissue in normal brains, in both the fixed and the unfixed state. The water content of the corpus callosum is somewhat higher than that in the fixed normal corpus callosum studied in this laboratory though not higher than in fresh, unfixed corpus callosum in another study (Stewart-Wallace, 1939). This difference is not statistically significant. The water content of the deep white matter of the hypertensive brains is significantly higher ($P < 0.01$) than that in fixed normal brains studied by us, the

TABLE I
READILY VOLATILE WATER (% WET WEIGHT) IN BRAINS OF
HYPERTENSIVE INDIVIDUALS

Case	Arcuate White Matter		Deep White Matter		Corpus Callosum		Cortex	
	A	E	B	F	C	G	D	H
1	77.2	76.6	72.0	71.4	70.8	71.2	84.0	83.6
2	79.8	79.2	76.8	76.4	76.0	75.8	86.8	87.0
3			73.0					
4	81.2	81.0	75.6	75.0	74.6	73.8	83.4	83.8
5	78.1	78.2	74.0	73.6	73.0	73.4	87.5	86.7
6	81.0	80.6	76.2	76.0	74.8	74.5	85.6	85.0
7	78.2	78.0	76.0	75.8	73.6	73.4	87.2	86.2
8	78.5	78.6	76.2	76.2	75.8	75.6	86.0	85.6
9	80.2	79.6	78.4	78.4	76.5	76.1	85.2	85.6
10	79.6	79.8	78.6	78.2	76.8	75.8	84.2	85.0
11			66.6					
12			72.7					
Median ¹	79.5		75.6		74.7		85.4	
Mean ¹	79.2		74.6		74.5		85.5	
Mean (normal)	79.0		71.2		73.3		85.4	

¹The duplicate values were averaged before calculations.

latter figure being like that reported in unfixed brains (Folch-Pi and LeBaron, 1957).

Histological study with the Luxol blue-P.A.S. technique was possible in 11 cases, the paraffin block having been lost in case 6. None of the tissues contained lakes of oedema fluid, as may be present in severe instances of acute oedema (Feigin and Popoff, 1962). With this myelin stain, pallor of the central portions of the white matter, contrasting with a normal depth of staining of the arcuate zone, was evident in two instances (cases 4 and 5). Histological studies with gold sublimate techniques were possible in only 10 cases, since the impregnation was not satisfactory in case 9. All of these showed regressive changes in the deeper portions of the white matter like those previously described and summarized in the introduction to this paper. In seven of these 10 cases (cases 3, 4, 5, 8, 10, 11, 12), the astrocytes in the arcuate zone were relatively normal, in contrast to the altered astrocytes in the deeper white matter. In the other three, they showed similar regressive changes. In four instances (cases 3, 8, 10, 11), the changes in the deeper astrocytes were thought to be acute.

COMMENT

The data indicate that the deep white matter, that portion of the brain most specifically affected in cerebral oedema, contains a significantly higher water content in hypertensive individuals than in normotensive individuals. No differences were noted between the water contents of cortex or arcuate white matter in the two groups, these tissues generally

FIG. 1

FIG. 2

FIG. 1. Deep white matter (case 3), showing regressive changes in astrocytes. Paraffin gold sublimate. $\times 500$.

FIG. 2. Arcuate white matter (same section illustrated in Figure 1). The astrocytes here are more nearly normal. Paraffin gold sublimate. $\times 500$.

being spared in cerebral oedema. There was a slight difference between the water content of the corpus callosum in the two groups: this difference is not statistically significant, but it is in accord with the observations that the corpus callosum is less completely refractory to cerebral oedema (Greenfield, 1939; Adachi and Feigin, 1966).

The magnitude of the change in the deep white matter, if due solely to an increment of water, is more clearly evident when the increment itself is calculated. For an increase in water content from 71.2% (mean normal) to 74.6% (mean hypertensive), 0.134 g. of water would have to be added to each 1 gram of white matter (13.4%). If this were a 1,200 g. brain with 50% white matter, the water increment would be approximately 80 g. or 80 ml. This is a considerable increment of volume to be associated with a condition in which no increment of intracranial pressure (Fishberg, 1954) or clinical abnormality is generally observed.

The water values cited really reflect the relative proportion of water and solids. Thus, the value 71.2% water in normal white matter indicates the

presence of 0.712 g. of water and 0.288 g. of solids in each 1 g. of tissue. The apparent water content could rise to that observed in the hypertensive brains, 74.6%, if the water were unchanged but some of the solids had been lost, as is indeed indicated by histological studies. Thus, the original 0.712 g. of water associated now with only 0.242 g. of solids, would result in the observed water value of 74.6%.¹ It should be noted that the decrement of solids, 0.046 g. per gram of white matter (4.6%), or 27.6 g. in a 1,200 g. brain with 50% white matter, is of lesser magnitude than the increment required

$$^1 \text{ Normal: } \frac{\text{Water}}{\text{Total}} \frac{0.712}{1} = 0.712 = 71.2\%$$

Hypertensive: Let x = increment of water

$$\frac{\text{Water}}{\text{Total}} \frac{0.712 + x}{1.0 + x} = 0.746 = 74.6\%$$

$$x = 0.134 \text{ g./g.}$$

or let y = decrement of solids

$$\frac{\text{Water}}{\text{Total}} \frac{0.712}{1.0 - y} = 0.746 = 74.6\%$$

$$y = 0.076 \text{ g./g.}$$

if the change in water concentration were due entirely to added water, and this loss in solids would not produce an increase in intracranial pressure. It is therefore more consistent with the observed absence of increased pressure than the alternative interpretation, and is probably the more important factor in the observed elevation of water concentration. The slight loss of tissue may not be clinically manifest. It may, however, be a factor in the pathogenesis of the dilated perivascular spaces seen so often in the white matter of hypertensive individuals. It should be recognized that these two factors are not mutually exclusive, and that both tissue loss and an absolute increase in fluid may be present simultaneously. Of greater significance is the realization that tissue loss is itself the result of an antecedent, transient or continuing episode of fluid increase, *i.e.*, cerebral oedema, related to the hypertensive disease. Whether some episodes of headache or other transient neurological symptoms, to which hypertensives are prone, are specifically related to episodes or acute cerebral oedema, is not established.

The histological studies suggest that the examination of astrocyte morphology with gold sublimate impregnations is a far more sensitive indicator of present or antecedent cerebral oedema than was suspected, and shows changes in tissues which appeared normal grossly and with other histological stains. The use of paraffin sections greatly facilitates studies with the gold technique (Naoumenko and Feigin, 1961). In any case, the profound regressive changes so evident in these hypertensive cases, and in other cases of cerebral oedema, may well result in a loss of solids of sufficient magnitude to account for part or all of the apparent increment of water content. There are, of course, many other conditions associated with regressive changes in astrocytes, and oedema may be implicated only when the changes as a whole suggest oedema. A sparing of the arcuate astrocytes associated with regressive changes in the deep white matter is strongly suggestive of oedema. The loss of myelin, which has been observed following episodes of cerebral oedema of great intensity, was minimal or absent in the tissues studied, there being central pallor which contrasted with the normal arcuate zone in only two instances. Such pallor is seen in acute oedema, reflecting a separation of fibres by oedema fluid, and as a sequel to oedema, reflecting loss of myelin.

This study appears to confirm the impression reported earlier that individuals with hypertensive disease tend to develop cerebral oedema with greater frequency and severity than do normotensive individuals. It emphasizes the constancy of the process. All but one of the cases being reported had water values greater than the mean of the normal popula-

tion. In the one exception, the water content, 66.6%, is considerably below all other values including those of the normal group, is most probably an error, but could not be justifiably excluded on such assumption. It is of interest that the difference between the hypertensive and normotensive groups is statistically significant even when this case is included. If it were excluded, the hypertensive group would contain a mean of 75.3% water in the deep white matter, a value close to the median and very probably more accurate. In addition to the elevated water values, morphological changes in astrocytes like those of past or present oedema were present in all 10 cases in which such studies were possible. These were acute in four cases, but not in six others. It is possible that the oedema is episodic, with periods of acute oedema being followed by periods of quiescence within which only the sequelae of the antecedent oedema may be recognized.

The data in the present and in the earlier studies suggest that the tendency to cerebral oedema is characteristic of the broad class of hypertensive individuals, and is not limited to those with severe hypertension, with 'malignant hypertension', or with 'hypertensive encephalopathy'. This tendency is evident in individuals in whom the blood pressure was only modestly elevated or, in the earlier study, had even returned to normal from documented hypertensive levels. The basic mechanism, therefore, may be related to an abnormality associated with hypertensive disease other than the hypertension itself. The same considerations appear to apply to the arteritic lesions in the brains of hypertensive individuals which may be the basis for the gross cerebral haemorrhages seen in such circumstances (Feigin and Prose, 1959).

This study has disclosed no effect of uraemia itself on the water content of the brains. Indeed, five of the 12 cases being reported (cases 8-12) had a blood urea nitrogen level above 50 mg.% terminally, but these cases do not differ significantly from the other seven. The same was true within the group excluded from the present study because of the presence of congestive right heart failure. The latter cases will be evaluated again, in part by comparison with a group of normotensive individuals in congestive failure. At this time, we are in a position to say that the water content of the deep white matter in these cases (mean 77.8%) is appreciably higher than in the group being described, and that the possibility exists that congestive failure in itself may produce or contribute to cerebral oedema.

In closing, a short comment may be warranted concerning the validity of the water analyses on tissues from fixed brains, a subject discussed at length in earlier papers (Feigin, 1966; Adachi and Feigin,

1966). We have presented evidence to show that the marked swelling reported in some other studies does not occur with the technique employed by us, *i.e.*, the fixation of the whole human brain in 20% formalin-1% acetic acid. The many normal values obtained attest to this conclusion. It is also well to note that cerebral oedema has been demonstrated in the brains of animals rendered hypertensive by experimental means (Byrom, 1954; Meyer, Waltz, and Gotoh, 1960; Rosenblum, Donnenfeld, and Aleu, 1966).

SUMMARY AND CONCLUSION

The water content and histological appearance of tissues of the brains of hypertensive individuals were compared with those of normal individuals previously studied. The deep white matter of the hypertensive individuals contained significantly more water than in normal individuals and showed histological changes like those of present or antecedent cerebral oedema. The cortex, arcuate white matter, and corpus callosum were essentially similar in the two groups. It is the deep white matter that is specifically affected in cerebral oedema.

These data suggest that hypertensive individuals in general tend to develop cerebral oedema, as was inferred from a previous study of isolated cases. This phenomenon is not restricted to cases of 'malignant hypertension' or of 'hypertensive encephalopathy'.

REFERENCES

- Adachi, M. and Feigin, I. (1966). Cerebral oedema and the water content of normal white matter. *J. Neurol.*, **29**, 446.
- Byrom, F. B. (1954). The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension. *Lancet*, **2**, 201-211.
- Doyle, J. T. (1960). Report of Subcommittees on clinical evaluation, blood pressure measurement and ECG interpretation. *Amer. J. publ. Hlth*, **50**, no. 10, Suppl., pp. 20-28.
- Feigin, I. (1966). The course and sequelae of brain edema. To be published in the *Transactions of the Workshop on Brain Edema of the World Federation of Neurology*.
- and Popoff, N. (1962). Neuropathological observations on cerebral edema: the acute phase. *Arch. Neurol. (Chic.)*, **6**, 161-160.
- , — (1963). Neuropathological changes late in cerebral edema: The relationship to trauma, hypertensive disease and Binswanger's encephalopathy. *J. Neuropath. exp. Neurol.*, **22**, 500-511.
- and Prose P. (1959). Hypertensive fibrinoid arteritis of the brain and gross cerebral hemorrhage; A form of 'hyalinosis'. *Arch. Neurol. (Chic.)*, **1**, 98-110.
- Fishberg, A. M. (1954). *Hypertension and Nephritis*. 5th ed., p. 802. Lee and Febiger, Philadelphia.
- Folch-Pi, J. and LeBaron, F. N. (1957). Chemical composition of the mammalian nervous system. In *Metabolism of the Nervous System*, edited by D. Richter. pp. 67-71. Pergamon Press, New York.
- Greenfield, J. G. (1939). The histology of cerebral oedema associated with intracranial tumours (with special reference to changes in the nerve fibres of the centrum ovale). *Brain*, **62**, 129-152.
- Jellinger, K. (1966). Discussion of paper by Feigin (1965). The discussion will be published in the transactions of the *Workshop on Brain Edema of the World Federation of Neurology*.
- Meyer, J. S., Waltz, A. G., and Gotoh, F. (1960). Pathogenesis of cerebral vasospasm in hypertensive encephalopathy. II The nature of increased irritability of smooth muscle of pial arterioles in renal hypertension. *Neurology (Minneapolis)* **10**, 859-867.
- Naoumenko, J. and Feigin, I. (1961). A modification for paraffin sections of the Cajal gold-sublimate stain for astrocytes. *J. Neuropath. exp. Neurol.*, **20**, 602-604.
- Rosenblum, W., Donnenfeld, H., and Aleu, F. (1966). Effects of increased blood pressure on cerebral vessels in micr. *Arch. Neurol. (Chic.)*, In press.
- Stewart-Wallace, A. M. (1939). A biochemical study of cerebral tissue and of the changes in cerebral oedema. *Brain*, **62**, 426-438.