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NEUROLOGICAL MANIFESTATIONS OF MALIGNANT HYPERTENSION

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Damage to the nervous system has long been known to be a common manifestation of hypertension, and, since the incidence of hypertension rises with age, hypertensive neurovascular disease is becoming of increasing importance in our ageing population (Wright and McDevitt, 1954a, 1954b; Brain, 1954a, 1954b). That nervous system involvement in malignant hypertension also occurs is well recognized (Keith, Wagener, and Kernohan, 1928; Rosenberg, 1940; Schottstaedt and Sokolow, 1953), but no detailed study of the clinical patterns in this form of hypertension is so far available in the literature. We therefore intend to present an account of the 73 patients with malignant hypertension complicated by neurological damage seen at Hammersmith Hospital during the period 1935-55.

We are aware of the limitations and shortcomings inherent in retrograde clinical studies, and it is possible that certain of the less obtrusive incidents have been overlooked. The general patterns and the more important events, however, are portrayed more faithfully.

Material

In a series of 190 cases of malignant hypertension which will be the subject of a general report (P. Kincaid-Smith, J. McMichael, and E. A. Murphy, in preparation), 79 patients were found to have involvement of the nervous system (Table I). Since, as shown later, the

TABLE I.—*Material Studied in the Present Survey*

Patients	Neurological	Non-neurological	Total
Known to be dead ..	65	96	161
Living	4	18	22
Untraced	4	3	7
Total	73	117	190

Cases exhibiting neurological features	79
Cases with unrelated neurological diseases ..	6
Cases with neurological complications of malignant hypertension	73

incidence of headache was the same in those with neurological abnormalities as in those without, headache was not considered necessarily to indicate nervous system involvement. In 6 of the 79 cases the findings were due to coincidental disease; thus three had an undiagnosed spinal cord lesion, two had long-standing "idiopathic" epilepsy, and the sixth an unrelated infantile hemiplegia. When these six patients were excluded the incidence of

nervous system involvement was 73 in 190 malignant hypertensives, or 38%, which approximates to the figure of 40% given by Vančura, Chytil, and Fialová (1956). It was found, moreover, that in 17 of the 190 the presenting manifestation of the malignant phase was neurological. Death was due to a nervous system lesion in 33 (51% of 65 with neurological features, and 20.5% of the 161 patients in the entire group who are known to have died).

Care was taken to exclude those patients in whom the malignant phase was not recognized until after recovery from the acute phase of the neurological episode. Some difficulty arose in two groups of patients: (a) Those in whom papilloedema was not recognized in life, and a firm diagnosis of malignant hypertension was based on pathological findings (three patients). Here the onset of the malignant phase was dated from the appearance of such manifestations as severe headaches, loss of weight, severe retinitis with soft white exudate, and a raised sedimentation rate. (b) Those in whom no definitive neurological episode occurred, the diagnosis being based on physical signs discovered in the nervous system, unaccompanied by any subjective symptoms (three cases). In such cases we have assumed that the damage occurred in the malignant phase unless history or previous hospital records suggested otherwise.

Classification of Cases

When the four living and the four untraced patients were excluded, the remaining 65 could be divided into three groups according to the clinical pattern (Table II).

Group 1. Immediate Neurological Fatalities.—Each of 16 patients had suffered one neurological episode and died of it. The clinical diagnosis of cerebral haemorrhage, which

TABLE II.—*Age and Sex Distribution of Groups in Present Survey*

Group	Males			Females			Total		
	Cases	Average Age	S.D.	Cases	Average Age	S.D.	Cases	Average Age	S.D.
1	7	54.6	11.0	9	38.4	14.2	16	45.4	15.3
2	18	50.2	10.1	14	38.9	17.2	32	45.2	14.7
3	7	52.7	8.1	10	50.9	9.2	17	51.6	8.8
Alive or untraced	1			7			8		
Total	33	51.8	10.0	40	43.5	16.0	73	47.3	14.3

was made in each case, was verified at necropsy in 13. In some, severe uraemia or cardiac failure was also present terminally. (a) Ten were known to have pre-existing malignant hypertension. (b) In four, the malignant phase of hypertension was announced by the cerebral event, the "benign" phase having been present for an average of 4.5 years. (c) In two there was no previous history of hypertension.

Group 2. Neurological Incident(s) with Non-Neurological Death.—Thirty-two patients had one or more lesions of the nervous system but died from a non-neurological cause such as uraemia, heart failure, etc. (a) Fifteen had focal cerebral features (hemiplegia in 8, dysphasia in 2, focal seizures in 2 (1 with cortical blindness), multifocal episodes in 1, and symptomless pyramidal signs in 2). Each event was probably due to a local area of cerebral ischaemia, but this was proved pathologically in only two. (b) Ten had generalized cerebral features (generalized convulsions in 6 (accompanying terminal uraemia in 3) and non-uraemic mental change in 4). (c) Two had primary subarachnoid haemorrhage. (d) Five had isolated seventh nerve palsy.

Group 3. Multiple and Ultimately Fatal Neurological Incidents.—Seventeen patients died of a cerebral event and each had suffered one or more previous neurological incidents. (a) One having had a subarachnoid haemorrhage, and later a peripheral facial nerve palsy, died of a pontine haemorrhage. (b) Sixteen had survived one or more focal cerebral lesions in the past (cerebral ischaemia in 14, cerebral haemorrhage in 1, and a facial palsy in 1). While the majority died of an intracerebral haemorrhage (verified at necropsy in nine), five succumbed to the effects of multiple softening manifested clinically as a pseudobulbar palsy in three.

Rosenberg (1940) has suggested a neurological grouping of cases of malignant hypertension into those with features of increased intracranial pressure, multiple miliary cerebral vascular lesions, or severe cerebrovascular episodes, with a fourth group to include the possible combinations of the three. Considerable overlap occurs, however, with this system, and our cases could not be fitted into it. The grouping used here indicates the several clinical patterns and possibilities that exist when malignant hypertension is complicated by involvement of the nervous system.

From our grouping it can be seen that cerebral haemorrhage is usually fatal and may occur as an isolated event (group 1) or after one or more episodes of cerebral softening (group 3b). It is also clear that the number of patients dying of a cerebral lesion (groups 1 and 3) equalled that of those who died of a non-neurological cause, having survived a neurological episode (group 2). Thus it appears that the liability to a further lesion was slightly but not significantly greater in those who survived the first incident than in those who had so far suffered no brain damage.

Individual Features

Accurate and detailed information concerning the neurological aspects of malignant hypertension is difficult to find in the literature, the only adequate studies being those of Rosenberg (1940) and Schottstaedt and Sokolow (1953). Furthermore, much confusion has been caused by the indiscriminate use of the term "hypertensive encephalopathy." Having presented a working classification of the cases, we

now consider the individual features in turn, employing the 65 cases and, where appropriate, the 4 patients still alive, and the 4 untraced (Table III).

Sex.—The whole series of 190 patients with malignant hypertension contained 86 females, of whom 40 (46.5%) had neurological features, compared with 33 out of 104 males (31.7%). The difference in incidence is significant ($\chi^2=4.3$; $P<0.05$).

Age.—The average age at the time of the first neurological episode in the malignant phase was 47.3 years; in males 51.8 years; in females 43.5 years (Table II). The higher average age in males, the average ages, and the distribution throughout the decades can be shown to be the same as in the patients without neurological features (see Fig.), from which it may be inferred that the risk of developing neurological complications does not vary with age, though the type of lesion may do so.

Age and sex distribution of patients with and without neurological manifestations.

Underlying Pathology.—Of the 65 patients known to have died, post-mortem examinations, partial or complete, at this or other hospitals, were performed in 59, and the brain was examined in 47. Owing to the absence or limited nature of the necropsies, the basic pathology of the hypertension could be determined with certainty in only 48 (Table IV). Com-

TABLE IV.—Basic Pathology of Hypertension in Cases Studied at Necropsy

Pathological Findings	Total		Neurological		Non-neurological		Percentage Difference (P.D.)	S.E.D.	P.D.
	No.	%	No.	%	No.	%			
Essential hypertension	56	47	24	50	32	45	5	13.5	0.4
Chronic pyelonephritis	23	19	9	19	14	20	1	16.7	0.06
Chronic glomerulonephritis	19	16	4	8	15	21	13	20.6	0.6
Other renal diseases	12	10	6	12	6	8	4	17.3	0.2
Miscellaneous	9	8	5	10	4	6	4	18.3	0.2
Total	119		48		71				

parison with a control group of 71 non-neurological cases of malignant hypertension showed that there were no statistically significant differences between the two groups—that is, that neurological complications are equally common in all the forms of malignant hypertension.

Headache

One of the commonest symptoms of malignant hypertension is headache (Schottstaedt and Sokolow, 1953; Fishberg, 1954), and we found it in 77% of our 73 cases. In a control group of non-neurological cases of malignant hypertension,

TABLE III.—Frequency of Neurological Manifestations

	No. of Cases	Percentage of Neurological Cases	Percentage of Total Series
Acute cerebrovascular episode	54	74	28
(a) Focal brain ischaemia	35	48	18
(b) Cerebral haemorrhage	28	38	15
(c) Primary subarachnoid haemorrhage	4	5.5	2.1
(d) Hypertensive encephalopathy	1	1.3	0.5
Mental disturbances	43	59	23
Convulsions	20	27	10.5
Cranial nerve palsies	8	11	4.2

the equivalent figure was 74.4%. Thus, as indicated above, headache cannot be considered to be, of itself, a specific neurological symptom, although it played a prominent part in many of our cases. In eight, it was the presenting symptom of the malignant phase, but, like Ferris (1952) and others, we found no clear relationship between the headache and the blood-pressure level.

The headache was described as severe in 32 (44%)—these included three cases of subarachnoid haemorrhage—moderate in 15 (21%), and mild in 9 (12%). Seventeen (23%) patients had never suffered from headache. Frequently the headache possessed the qualities noted by Janeway (1913) and Wolff (1948): bursting and throbbing in character, frontal or occipital in site, worse on rising in the morning and improving as the day progressed, and commonly associated with nausea. Like Bechgaard (1946), however, we did not find it always characteristic. Moreover, by confining the use of the word "migraine" to the classical syndrome, we could not substantiate the claims of Janeway (1913) and Gardner, Mountain, and Hines (1940) that these patients often have a previous history of this condition; only one such patient was found in the entire series.

Further details of this important symptom will be discussed elsewhere (Kincaid-Smith *et al.*, in preparation).

Giddiness

Following the definition of Gowers (1888, p. 97) and the advice of others (Symonds, 1952), we have considered the terms "vertigo," "giddiness," and "dizziness" interchangeable. It was found that of the 40 patients who had been specifically questioned about this symptom, 16 (40%) said that they had experienced it at one time or another during the malignant phase. In a like group of non-neurological patients the percentage was 23. The difference (17%) is not quite statistically significant. Dizziness was never severe, nor did it persist for long periods. The incidence of cerebrovascular attacks—which occurred in half—and that of fits, was not greater than in the group without dizziness. It seems, therefore, that although dizziness is sometimes a herald sign of nervous complications it is of no help in predicting the form that they will take.

Other authors dealing with large groups of unselected hypertensive patients have given varying incidences of dizziness (Saracoglu, 1939, 32.2%; Janeway, 1913, 18%). Bechgaard (1946) claimed that it is a commoner symptom of hypertension than headache.

Mental Disturbances

Prolonged disturbances of the mental state, including impairment of consciousness, occurred during the malignant phase in 43 (59%) of 73 patients; in none of these was a detailed psychiatric appraisal undertaken. Alteration of consciousness was present in 23 (32%), excluding transient impairments due to epileptic seizures of minor cerebrovascular accidents. In 16 the cause was a fatal cerebral episode—proved to be a cerebral haemorrhage in the 14 in whom post-mortem examination of the brain was permitted. Terminal uraemia or congestive failure was responsible in the remaining seven.

The remaining 20 (27%) had varying degrees of disordered cerebration and constituted 10.5% of the 190 cases of malignant hypertension. The seven patients with terminal heart failure or uraemia mentioned above may also be considered here, because various mental abnormalities preceded the terminal coma. Only one patient had a psychological disturbance as the presenting symptom of the disease; the picture was that of a slowly progressive dementia, similar to that in the cases of Goodman (1949), but unlike the schizophrenic type of illness in the patient of Adkins, Fahr, and Bernstein (1955).

The mental changes in nine cases occurred in conjunction with a focal cerebral lesion, usually an area of softening; and they were present immediately after the ictus in each. Confusion persisted in some until death; in others it

gradually subsided. One patient had recurrent spells of depression, confusion, and emotional lability following a stroke. Only three of the nine were severely affected, and they each developed a progressive dementia, on account of which two were committed to mental institutions. The cerebral lesions in these patients were in the dominant hemisphere, and the association of impairment of language function, which was present in these as in other cases with mental changes, contributed to the clinical picture of dementia.

A further group of five patients had personality changes, emotional lability, memory defects, confusion, and varying degrees of pseudobulbar palsy. At necropsy multiple areas of cerebral softening, usually small in size and distributed mainly in and near the basal ganglia, were found. In most respects they resembled the cases described by Hughes, Dodgson, and MacLennan (1954), although only four of those had malignant hypertension. The ages of this group (60–68 years, average 63.6) were considerably higher than in the entire series, and presumably cerebral arteriosclerosis played an important part in the production of the clinical picture. This finding disagrees with the suggestion of Hughes *et al.* (1954) that the height of the blood pressure is more important than the age of the patient. We could demonstrate no correlation between the severity of the clinical findings and the degree of hypertension.

The remaining six patients had no clinical evidence of focal brain lesions, either single or multiple. One of them developed mild mental changes after a subarachnoid haemorrhage (Walton, 1953), but although these cleared up they returned with terminal cardiac failure. Another had post-epileptic confusional states which later became permanent. In the other four an abnormal mental state was constantly present with periodic exacerbations, thus resembling the case described by Rosenberg (1940, Case 9). Depression, found by Bechgaard (1946) in 7% of unselected hypertensives, was present in one of our cases before the malignant phase. Unlike the patient of Vigne and Le Pourhiet (1951) he was not improved by electric convulsion therapy, and remained unchanged when malignant hypertension supervened. Ganglion-blocking drugs, however, brought about considerable mental improvement. Another patient had "menopausal" melancholia, which seemed to improve as the disease advanced. Finally, in one case there was progressive dementia with obsessional features, and certification became necessary. The brain was not examined in any of these cases, but Rosenberg (1940, Case 9) found numerous small infarcts throughout the white matter and basal ganglia.

The average age of the patients with mental abnormalities was 57.7 years, compared with 47.3 for the whole series. It thus again seems possible that cerebral arteriosclerosis and other "senile" cerebral changes may be important factors in these cases, and the duration of the hypertension may also be of importance. In none of these cases was there a close relationship between the levels and fluctuations of the blood pressure and the altered cerebration, except in one patient, perhaps, suffering from paranoid delusions, who was more rational every time her blood pressure was lowered by pentolinium, but who never at any time reached a normal state. In all, two of our patients were improved by methonium therapy. Adkins *et al.* (1955) report similar results with reserpine, which, however, has a much more complex action, including direct effects on the brain (Pletscher, Shore, and Brodie, 1956).

Convulsions

Schottstaedt and Sokolow (1953) reported convulsions in 17.3% of 104 patients with malignant hypertension. Twenty of our patients experienced some type of epileptic phenomenon during the course of their disease—that is, 27% of the neurological series or 10.5% of the entire group. Eleven (15%) had generalized and 9 (12%) had focal attacks. Those with generalized convulsions had an average age of 45.8 years at the time of diagnosis, and those with focal attacks 45.3 years. Keith *et al.* (1928) found that fits were commoner

in malignant hypertensives under the age of 40 than in those over. In ours, 8 out of 17 (47%) under the age of 40 had fits, compared with 12 out of 50 (24%) over the age of 40. The differences are suggestive but not significant ($\chi^2=2.2$; $P < 0.2$).

In 9 of the 20 cases (7 generalized, 2 focal) uraemia was present at the time of the fit. The frequency of convulsions in 119 uraemic patients is therefore 7.6%, which is higher than that found in a random series of uraemic patients (Knutson and Baker, 1945; Oppenheimer and Fishberg, 1928). Schottstaedt and Sokolow (1953) made similar observations. The combination of renal failure and hypertension seems more likely to produce convulsions than either separately.

The seizures in three patients accompanied a terminal cerebral catastrophe. In two they were focal, and at necropsy were found to be due to subcortical cerebral haemorrhages, whereas in the one with general attacks a massive haemorrhage into the basal ganglia was present.

Only eight patients (11% of the series) thus experienced attacks in a non-uraemic and non-terminal state. Five had focal seizures and in each they were associated with a local cerebral lesion, shown at necropsy in four to be an area of softening. In the fifth, on whom no post-mortem examination was performed, epileptic phenomena were closely related to the administration of ganglioplegic drugs, but in the others they began one to eleven months after the cerebrovascular ictus. This time relationship corresponds closely with that given by Gowers (1893), and more recently by Dodge, Richardson, and Victor (1954), who have pointed out that convulsions following cerebral infarction are commoner than hitherto supposed. Their patients survived longer than ours, but they were all normotensive. Our patients died an average of three months after the first fit. It is usually said that convulsions are commoner with cerebral haemorrhage than with either thrombosis or embolism (Aring and Merritt, 1935; Millikan, 1955). This applies to their occurrence during the acute phase, whereas after the recovery from it the frequency is greater in cerebral softening (Gowers, 1888, p. 401; Richardson and Dodge, 1954).

The remaining three patients who had fits, but were non-uraemic and not in a terminal state, had the generalized type. A focal cerebrovascular episode had not occurred, and in the only case which came to necropsy no cause for the convulsions was found, though the examination was limited. This patient developed uraemia terminally, but the fits did not recur. The other two are still alive, but have ceased to have attacks. The aetiology of the convulsions in these three patients is thus unknown, but in none could true hypertensive encephalopathy be incriminated.

It is of interest to note that the two patients with long-standing "idiopathic" epilepsy, and excluded from this series, did not experience an aggravation of the convulsions in the presence of malignant hypertension. It is also to be noted that, as Jefferson (1955) points out, epilepsy associated with hypertensive disease is less persistent than that produced by a cerebral neoplasm.

Acute Cerebrovascular Episodes

Events suggesting acute brain damage occurred in 54 out of 73 cases (74%). The equivalent figure given by Schottstaedt and Sokolow (1953) is 42%, but they give no pathological data in support of this. Peet and Isberg (1948) reported cerebrovascular accidents in only 20% of 162 cases of malignant hypertension, but they may have been considering only the more obvious and severe episodes. Jaffé (1937) also cited an incidence of 20% when dealing with pathological material from benign and malignant essential hypertension, yet Janeway (1913) gave 52.3% in his large series of unselected hypertensives.

Cerebrovascular attacks could be divided into focal brain ischaemia, intracerebral haemorrhage, primary subarachnoid haemorrhage, and "hypertensive encephalopathy." Some patients had more than one type of lesion.

Focal Brain Ischaemia

Under this heading are included all who suffered a local area of brain damage, which we considered could not be attributed to haemorrhage. The difficulty of differentiating between haemorrhage and softening in some patients (Aring and Merritt, 1935) is, however, recognized. Clinically, these patients had a "stroke," usually shown at necropsy to be due to the effects of local ischaemia of brain tissue with the production of an area of softening. Although minute neuropathological study of the brain had not been performed in any of our cases, it is likely that the infarction represented the end-results of one of three phenomena—thrombosis, embolism, or local insufficiency. The last-named seems to explain satisfactorily those cases in which a process obstructing an artery cannot be detected at necropsy despite a careful search. Thus transient neurological events indicating a focal brain lesion may be the result of ischaemia produced by variations in blood pressure within the territory of a cerebral artery, the lumen of which has been partially occluded. This is illustrated by obstruction of the internal carotid artery (Denny-Brown, 1951), and the part played by changes in the systemic blood pressure has been emphasized by Corday, Rothenberg, and Putnam (1953). The importance of cerebral emboli is also considerable (Pickering, 1948; Adams, 1955, p. 27). The mechanism of thrombosis, embolism, and cerebral insufficiency can be readily understood in terms of the known facts of cerebral physiology and pathology without invoking the hypothetical entity of "angiospasm" as a primary aetiological factor. That it occurs cannot be denied; that it can cause severe focal ischaemia has never been proved.

Altogether 35 patients (48%) gave evidence of focal brain ischaemia at one time or another during the course of their disease. The figure 13% given by Jaffé (1937) refers only to deaths from cerebral softening. In three of our patients focal clinical manifestations were absent; one presented with a spontaneous subarachnoid haemorrhage, found at necropsy to be due to an area of softening communicating with a lateral ventricle, while two had multiple scattered areas of infarction and a clinical picture of mental derangement similar to that in the cases of Hughes *et al.* (1954), but without the pseudobulbar features. The latter type of case has already been considered with three similar examples. The signs of residual hemiplegia occurred in one patient in whom there was no history of an acute episode. In this regard, Cohen (1955), when dealing with cerebrovascular disease as a whole, found that cerebral infarctions were clinically silent in 40% of cases.

The remaining 30 patients (10 males, average age 51.2 years; 20 females, average 50.3 years; average for the whole group, 50.9 years) gave clear evidence of focal cerebral episodes which clinically and at necropsy in 14 could be distinguished from the intracranial haemorrhage. Eight, however, had been treated with ganglioplegic drugs, in six of whom the events were closely related to their administration. Thus, one man experienced cortical blindness while in an induced hypotensive state, but recovered when the previous blood pressure was restored. The residual symptoms and signs were minimal in all but one of these six; one died of cerebral haemorrhage, two of uraemia, two are still alive, and the cause of death is unknown in the sixth.

The 25 untreated patients are considered in detail. Twelve had solitary episodes, and in 13 there was more than one episode each. The type and frequency of the attacks were as follows:

Hemiplegia (with or without dysphasia or sensory phenomena)	13
Bilateral pyramidal tract signs with pseudobulbar features	5
Dysphasia alone	3
Disturbance of the visual pathways	2
Brain-stem lesion (Millard-Gubler syndrome)	1
Monoplegia	1

Involvement of the brain stem and cerebellum was relatively uncommon, and a bulbar syndrome such as Lafon,

Pages, Minvielle, and Barjon (1955) have described in malignant hypertension was not encountered.

In six with double episodes, considerable recovery followed the first, but little occurred after the second. The survival in the 12 cases with single attacks varied from 4 days to 2½ years (average 12.2 months).

Twelve of the 25 were in group 3*b*, since they had had a focal cerebral episode and died from a neurological lesion, shown at seven of the eight necropsies to be due to cerebral haemorrhage. Areas of old softening were also present in some of these brains. Ten patients were in group 2*a*, being similar to those in group 3*b* but having died from non-neurological causes.

Cerebral Haemorrhage

Cerebral haemorrhage was demonstrated at necropsy in 23 cases—that is, 14.3% of the 161 patients known to have died. In fact, the incidence is certainly higher than this because those cases in which a firm clinical diagnosis was made but in which there was no pathological confirmation are not included. If these are included, 43% of the neurological patients succumbed to this lesion. It is a rather higher incidence than that recorded in unselected hypertension (Paullin, Bowcock, and Wood, 1927, 7.2% ; Jaffé, 1937, 7.2% ; Clawson, 1928, 11.5%). As a fraction of the 47 cases in the neurological group whose brains were examined at necropsy, it constitutes 49%—compared with 4 out of 15 (27%) who died of neurological causes in the series described by Rosenberg (1940).

Thirteen of the cases had sustained no previous neurological incident (group 1), whereas 10 in group 3 had survived earlier episodes shown at necropsy to be due to areas of cerebral softening in seven and to a small intracerebral haemorrhage in one.

The average age was 48.2 years (12 females, average 43.5 years; and 11 males, average 53.4 years). The clinical manifestations of the lesions were similar to those occurring in the "benign" phase of hypertension, including the prodromata described by Taylor and Page (1945) in a series of "benign" essential hypertensives. Headache had been present before the ictus in 19 out of the 20 patients in whom such information was available. Twelve were dead within 12 hours of the apoplexy and all but two within one week. As in the case of Meerloo (1935) the malignant hypertension announced itself by cerebral haemorrhage in six cases (group 1*b* and 1*c*). Differentiation in these cases from intracranial bleeding due to another cause is important, especially as papilloedema is known to occur with intracerebral haemorrhage (Bouveret, 1895). In two the first and only clinical event was the ictus, but we are certain that the papilloedema in these patients was due to malignant hypertension rather than an intracranial space-occupying lesion.

The site of the intracranial bleeding in the 23 cases was as follows: basal ganglia in 57%, cerebral white matter in 22%, pons in 13%, cerebellum in 4%, and mid-brain in 4%.

This corresponded more or less with that recorded by Greenfield (1938), Adams and Eecken (1953), and Cohen (1955) in all types of hypertensive and arteriosclerotic patients, although Epstein (1951) has claimed that pontine haemorrhage is commoner in those with the more severe forms of hypertensive cardiovascular disease. In the latter respect, we have been careful to consider only those cases with primary haemorrhage into the pons: those occurring secondarily to bleeding into the internal capsule (Attwater, 1911) or increased intracranial pressure (Cannon, 1951) have been excluded. Although haemorrhage into a pre-existing area of brain infarction may have taken place in some of our cases, we have no direct proof of this. It appeared that those who had had a softening and then a terminal haemorrhage survived longer than those with a single haemorrhage, which also transpired from Rose's (1948) series. In view of the theory that intracerebral bleeding is due to rupture of an unsupported artery in an area of recent softening (Globus and Strauss, 1927; Globus 1938), a search was made for bleeding elsewhere in the body in the patients

with cerebral haemorrhage, in those sites where the blood vessels are poorly supported by connective tissue. Epistaxis and haematuria were found to have the same incidence in the neurological and in the non-neurological group.

It seems, then, that cerebral haemorrhage giving rise to focal clinical signs must continue to have a sinister reputation. In 22 out of 23 cases it was rapidly fatal, and the only survivor succumbed to a similar incident later.

The multiple miliary haemorrhages described by Rosenberg (1940) were found in six patients, and in each of the four in whom details of the terminal events were known renal failure had been present. The five patients in whom this phenomenon was encountered by Rosenberg (1940, Cases 2, 3, 8, 16, and 17) likewise had marked nitrogen retention. In all our cases the lesions were recent and corresponded to those described by Knutson and Baker (1945) in miscellaneous uraemic brains. Their relationship to pre-existing neurological features which were in no way distinctive is therefore doubtful. On occasion both haemorrhages and softenings of symptomless, miliary type may be present, and these are dealt with below. The relative importance of degenerative changes in cerebral vessels and cardiac as well as renal failure has not been evaluated, but they are no doubt of aetiological significance.

Primary Subarachnoid Haemorrhage

Primary subarachnoid haemorrhage had occurred in four cases, but in one it had taken place eight years before death, at a time when the blood pressure was known to be normal. Of some interest is the fact that the responsible aneurysm in this case was found intact at necropsy, despite the grossly increased tension to which it was exposed in life. The other three had an average age of 43 years and a mean survival of five months. The bleeding did not differ clinically from that seen in normotensive patients except that preceding headaches were more common. Only one patient had focal neurological signs. In one the haemorrhage was the first clinical evidence of the malignant phase of hypertension which was diagnosed on admission. Although papilloedema occurs in about a sixth of all cases of spontaneous subarachnoid haemorrhage (Manschot, 1954) and may be observed within hours of the ictus (Ballantyne, 1943, Case 1) the retinal changes in our case indicated malignant hypertension, which was confirmed at necropsy. One died from an independent pontine haemorrhage, and the other two from non-neurological causes. In none was an intracranial aneurysm found, but it is certain that the subarachnoid blood was not secondary to an intracerebral haemorrhage, a cause of confusion in the first case in Ballantyne's (1943) series.

A further three patients (6% of the 47 whose brains were examined) were found to have small unruptured intracranial aneurysms, and these too seemed to have survived the effects of high arterial tension without rupture. This incidence is higher than in the normotensive population, and though the numbers are too small for firm conclusions to be reached it does raise the question of the role of hypertension in the production of these lesions, for which some evidence is already available (Hicks and Black, 1949; and others).

Hypertensive Encephalopathy

"Hypertensive encephalopathy" is a term introduced by Oppenheimer and Fishberg (1928) to describe the acute cerebral episode manifested by increasing blood pressure, headache, and drowsiness, accompanied at times by vomiting, visual impairment, convulsions, and focal neurological features. Patients who had severe hypertension but were not uraemic died occasionally in an attack. Like Volhard (1935), Oppenheimer and Fishberg thought that the basic lesion was cerebral oedema, and that this was produced by "vasospasm." There has been considerable confusion ever since the condition was described, mainly because these and other authors have included in this entity many of the features that are in fact the result of focal brain ischaemia,

and also because of the vague and conflicting conceptions of the pathogenesis and the pathological findings. Unfortunately, the term is often used nowadays to include any cerebral event occurring in a hypertensive patient.

We have studied our patients carefully, and can find only one in whom attacks occurred that were akin to the original account given by Volhard (1918) and by Oppenheimer and Fishberg (1928); all the other patients with acute episodes apparently corresponding to "hypertensive encephalopathy" had either uraemia or focal cerebral ischaemic incidents. Furthermore, Schottstaedt and Sokolow (1953) do not mention an example when describing 104 cases of malignant hypertension. Jefferson (1955) mentions but does not describe two cases with acute hypertensive crises in 36 hypertensives with retinal changes.

This aspect of malignant hypertension will be dealt with elsewhere (Clarke and Murphy, in preparation), but we would point out here the need for greater clarity of thought concerning acute cerebral episodes in this disease. The term "hypertensive encephalopathy" should be reserved for those patients suffering acute attacks such as Volhard (1935) described, and it would seem that these are very rare. Other events which are probably due to focal brain lesions of various kinds must be investigated more fully, both clinically and pathologically, and by means of the electroencephalogram as well as by employing more adequate clinico-pathological correlation.

Cranial Nerve Palsies

Eight patients had isolated cranial nerve palsies: five have been considered already in group 2*d*; one is still alive; one is untraced; and one, having other neurological lesions, has been included in group 3.

Seven had an affection of the facial nerve on one side, and the eighth had a unilateral abducens nerve palsy. Recovery of function was usually incomplete, but in each case there was no evidence of concomitant neurological lesions. The pathogenesis of these events is unknown, although at least one patient was suffering from periarteritis nodosa. This unusual but well-authenticated complication of malignant hypertension (Griffith, 1933) will be dealt with in detail elsewhere (Clarke, in preparation).

Cerebrospinal Fluid

The C.S.F. was examined in 42 patients (67% of those dead and traced), and in only six was it normal in all respects. In four of the latter, however, the lumbar puncture had been carried out some time after a cerebral incident, when an abnormality would probably not be expected; and two had isolated cranial nerve palsies (group 2*d*).

Of the remaining 36 patients, a high C.S.F. pressure (200 mm. of C.S.F. or over) was recorded in 29 (67%), which approximates to the 62% reported by Schottstaedt and Sokolow (1953). In 11 patients this was the only abnormality in the fluid, but in half of these it occurred in association with an acute cerebral episode, of which only one was thought to be a case of true hypertensive encephalopathy. The pressure in this instance was, however, only moderately raised (245 mm. of C.S.F.) despite the claims of Oppenheimer and Fishberg (1928) that intracranial hypertension is an invariable accompaniment of this condition. Although papilloedema was present in the vast majority of our cases, an elevation of the C.S.F. pressure was frequently absent; the possibility of foramenial herniation of the brain (Blackfan and Hamilton, 1925; Lecucq, 1945) producing this disparity seems most unlikely. In 10 out of 20 patients with no neurological features, the pressure was over 200 mm. of C.S.F., and headache, which was present in all but one, was severe in only 50% of them. This lack of exact correlation was found by Block and Oppenheimer (1924) and Fishberg and Oppenheimer (1930), although, as Shelburne, Blain, and O'Hare (1932) and Pickering (1934) have shown, patients with malignant hypertension on the whole tend to have higher C.S.F. pressures than those in the "benign" phase. Taylor, Corcoran, and Page (1954),

from an extensive study, support these conclusions with statistical proof. In none of our cases had the C.S.F. pressure and the arterial pressure been recorded synchronously.

Although 16 patients had a blood-stained or xanthochromic C.S.F., which resulted from an intracerebral haemorrhage in 14 and from a subarachnoid haemorrhage in 2, 10 of the former and both of the latter had C.S.F. pressures of 300 mm. of C.S.F. or over.

The C.S.F. was examined in 62 patients with malignant hypertension (42 with neurological lesions and 20 without them), but no example of a pleocytosis could be found, despite the fact that many patients had uraemia, and that such C.S.F. changes may occur in this state (Madonick, Berke, and Schiffer, 1950).

Only nine patients (21.4%) had an elevated C.S.F. protein content in the absence of previous bleeding into the fluid; in three this was above 100 mg. per 100 ml. of fluid (100, 110, and 125 mg. per 100 ml.), which occurred in the case of hypertensive encephalopathy and two cases of focal ischaemia. With regard to the latter, it should be noted that Adams (1955, p. 96) has observed a higher C.S.F. protein in cerebral softening due to malignant hypertension than in that due to other causes, and the results of Schottstaedt and Sokolow (1953) were more impressive than ours, although it is not clear that they excluded blood-stained fluid. Aring and Merritt (1935), on the other hand, dealing with 245 cases of cerebral haemorrhage and thrombosis, found the level above 100 mg. per 100 ml. in only one non-bloody fluid. The reason for this is not clear, but it is important to observe that 7 out of 16 patients without neurological complications had an increased protein level. Taylor *et al.* (1954), however, when comparing the C.S.F. protein in benign and malignant hypertension, found little difference between the two. It is not clear how many had neurological features.

Unlike Schottstaedt and Sokolow (1953) we were unable to evaluate the therapeutic aspects of lumbar puncture, because in our material it had been used only as a diagnostic procedure. Untoward effects such as reported by Shelburne *et al.* (1932), Riser, Planques, and Becq (1938), and Schottstaedt and Sokolow (1953) were not encountered.

Additional Pathological Findings

Certain pathological findings in the brains of patients dying from malignant hypertension must be dealt with in more detail.

Some of the cases described by Rosenberg (1940, Cases 5 and 14) and included in his first group, as well as others termed "hypertensive encephalopathy" by Scheinker (1943, Case 1), cannot be included in the classification that we have suggested. We did not consider them to be primarily neurological problems, for, despite the apparent features of raised intracranial pressure, this could not always be demonstrated by necropsy or by C.S.F. pressure. In addition, Pickering (1934) has shown the occasional lack of correlation between the latter and the symptoms of severe arterial hypertension (papilloedema, convulsions, coma, and headache). These patients usually had obvious evidence of cardiac and renal insufficiency as well as hypertensive retinopathy, and, despite the similarities, should not be confused with cases of intracranial neoplasm. Riley and Elsberg (1926), Grant (1932), Vallat (1938), and Cruz (1952), have, however, discussed the possibility, and Jefferson (1955) has considered the clinical, radiological, and electroencephalographic differences between hypertensive brain disease and cerebral tumour.

When the brain in this type of malignant hypertension is examined carefully, oedema, scattered minute haemorrhages, and areas of softening have been detected (Rosenberg, 1940; Scheinker, 1943). It seems likely that these are mainly terminal changes, and, as admitted by Rosenberg (1940) when discussing a similar case (Rosenberg, Keith, and Wagener, 1938), may not announce themselves clinically, and,

as already suggested, may be related to renal failure. It is also possible that many of the older foci of destruction found in the brains of these patients are also silent if very small and situated in an non-eloquent area.

In 42 of our non-neurological patients the brain was examined. In 26 it was said to be normal, but in most instances histological examination had not been carried out. Eleven brains were thought to be oedematous, and in five there were multiple miliary areas of haemorrhage or softening, or both. In each of the 16 cases the patient had died in a state of severe uraemia.

Much confusion exists concerning cerebral oedema, mainly because of deficiencies in pathological knowledge. It was considered to be present in seven of our patients (15% of those whose brain had been examined and who showed clinical evidence of neurological involvement), but only macroscopic assessment was made. Like the 11 in the non-neurological group, in each patient death had been in part due to severe renal insufficiency. Eleven of Rosenberg's (1940) 17 patients had some evidence of cerebral oedema, but in all except one the blood urea was raised. The role of uraemia in the production of cerebral oedema has long been the subject of speculation (Traube, 1871; Cushing and Bordley, 1908; Blackfan and Hamilton, 1925), but further elucidation of the problem is called for. Of our seven patients, only one had a lumbar puncture within 24 hours of death, and the C.S.F. pressure was normal. Rosenberg (1940) likewise could not detect a constant relationship between the C.S.F. tension, the degree of papilloedema, the urea content of the blood, and cerebral oedema. Taylor *et al.* (1954), when studying the C.S.F. pressure in malignant hypertension, used the Ayala index in support of this conclusion.

The brains of some of our neurological patients were described as normal, despite striking abnormalities of function during life, but Allbutt (1915) and Rosenberg (1940) have each emphasized the importance of closer study. It is possible that the apparent lack of anything pathological in some patients dying of "hypertensive encephalopathy" (Volhard, 1935) is due to inadequate histological investigations, an accusation that has already been brought forward by Adams and Eecken (1953).

Prognosis and Treatment

For a number of reasons it is very difficult to assess the prognosis in this group. Some of the patients had already suffered damage to the nervous system before entering the malignant phase, or before it was recognized; in 3 out of 65 no papilloedema was noted at any stage, and therefore the date of onset of the malignant phase could not be estimated with accuracy. In many there was advanced renal or cardiac disease in the presence of some relatively benign neurological complication, and it was the former rather than the latter that was important from the point of view of prognosis. The material was not itself homogeneous—a massive cerebral haemorrhage is obviously an immediate threat to life, while a facial palsy carries no added risk at all. Any attempt at splitting the cases into homogeneous groups results in groups too small for any kind of valid statistical analysis. Accordingly, from the material studied the following have been excluded: those in whom papilloedema was not recognized during life (3 cases); those found to have physical signs in the nervous system but who gave no history of an acute incident (3 cases); those who developed neurological features terminally only, in whom no therapy in the way of sympathectomy or ganglion blockade would be considered (18 patients); and those, other than patients still alive, whose fate is unknown (4 cases).

The remaining 45 patients were divided into three groups: (A) little or no cardiac involvement, and blood urea under 100 mg. per 100 ml. at the time of the neurological episode (13 cases); (B) a history of dyspnoea on moderate effort or less, or paroxysmal nocturnal dyspnoea with a blood urea of 100 mg. per 100 ml. or less at the time of the episode

(24 cases); (C) blood urea over 100 mg. per ml. with or without severe cardiac damage at the time of the neurological episode (8 cases).

It is felt that these probably represent fairly homogeneous groups as regards prognosis, and they are of fairly equal size. There were 22 treated and 23 untreated cases.

The findings are analysed in Table V. Some of the survival times are incomplete among the treated group, because the patients are still alive; the figures quoted therefore

TABLE V.—*Survival of Patients with Neurological Manifestations*

Group	Treatment	Male	Female	Total	Average Survival (Months)	Still Alive	Cause of Death	
							Neur.	Non-neur.
A	None	3	4	7	7.7 ± 4.3	0	4	3
	Nephrectomy	0	1	1				
	Sympathectomy	1	1	2	13.9 +	1	3	2
	Methonium	3	0	3				
B	None	5	4	9	5.0 ± 2.7	0	2	7
	Sympathectomy	2	2	4	17.5 ± 10.9	0	1	3
	Methonium	7	4	11	17.6 +	4	4	3
C	None	1	6	7	2.9 ± 1.3	0	2	5
	Methonium	1	0	1	3.0	0	0	1

For explanation of the grouping see text.

represent the worst possible outcome of treatment and may improve. It will be apparent that with the exception of group C the age and sex composition is similar enough to present no distortion from this cause.

The numbers are small and the results very difficult to assess. It is clear that all forms of treatment are beneficial except in the presence of severe renal damage. Methonium therapy has produced the best results and would appear to be the treatment of choice. Not only are the immediate dangers less than with sympathectomy, but if the lowering of the blood pressure proves deleterious it can easily be reversed, or produced to a less drastic degree. No doubt those rare cases of hypertension due to operable primary disease should still be treated surgically; but should the blood pressure rise again later—as it usually does in these cases—methonium therapy can be used with advantage. We feel that the drugs at present available should be administered parenterally rather than by mouth, as their absorption is more certain, and catastrophic and unexpected falls in blood pressure—which might be well enough tolerated in patients with an intact cerebral vasculature—with their attendant dangers, may thus be avoided. The future may produce more trustworthy oral drugs.

It is quite common for patients with overt or latent cerebral vascular disease to experience temporary exacerbation of their symptoms when the blood pressure is lowered. Finnerty, Witkin, and Fazekas (1954) have shown that this is due to diminished cerebral blood flow, arising from failure of adaptation of the cerebral vascular resistance. They showed, moreover, that adaptation is less readily effected in the "malignant" than in the "benign" hypertensive.

Summary

A study of the neurological features which were present in 73 out of 190 cases (38%) of malignant hypertension has been made.

The 65 patients known to have died could be grouped clinically into: group 1, those dying from a single neurological episode; group 2, those suffering a neurological lesion but dying from a non-neurological cause; and group 3, those who suffered more than one cerebral lesion and died because of them.

Individual manifestations of involvement of the nervous system have been analysed. Unlike giddiness, headache was no commoner than in the non-neuro-

logical group; 27% of the patients suffered from epileptic seizures, but in almost half uraemia was present; 27% had an abnormal mental state, usually associated with focal or generalized vascular lesions.

Three-quarters had an acute vascular episode (focal ischaemia in 48%, intracerebral haemorrhage in 38%, and subarachnoid haemorrhage in 5.5%); and some had more than one type of lesion. Criticism is levelled at the frequent misuse of the term "hypertensive encephalopathy," which should be reserved for the syndrome as described by Volhard; it seems to be very rare, and was found in only one of our cases.

An attempt should always be made to determine the cause of each cerebral event, and the term "focal brain ischaemia" used in appropriate cases.

There were eight isolated cranial nerve palsies (facial nerve in seven, abducens in one).

The C.S.F. pressure and contents were normal in 6 out of 42 cases. High pressure was found in 29, blood-staining in 11, and elevated protein content in 9 non-bloody fluids; some had more than one abnormality.

Treatment appears to have prolonged life where severe renal damage was not present at the start of treatment. The survival in this group when untreated averaged less than a year. Ganglioplegic drugs seemed to be more effective than sympathectomy.

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ANALGESIC SUPPLEMENTS TO NITROUS OXIDE ANAESTHESIA

A REVIEW

BY

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The many advantages of nitrous oxide were for a long time overshadowed by its weak anaesthetic properties and by its inability to produce muscular relaxation. Although widely used for analgesia in midwifery, for anaesthetic inductions, and as one of the vehicles to carry the vapour in ether anaesthesia, nitrous oxide could not be relied upon to produce adequate anaesthesia in every case, even in well-premedicated patients.

The short-acting barbiturates awakened a new interest in nitrous oxide. Within a few years nitrous oxide and oxygen anaesthesia supplemented with thiopentone had become an established technique. For operations which required no muscular relaxation this combination seemed ideal, since it was easy to administer, afforded the patient a pleasant induction, and allowed the surgeon to use diathermy. Although thiopentone was a potent hypnotic, its lack of analgesic properties and its slow degradation in the body led to frequent complications, especially in prolonged operations that required large doses of the barbiturate. As experience accumulated, the triad of respiratory depression, circulatory failure, and prolonged post-anaesthetic recovery caused the technique to be regarded more critically.

Many anaesthetists added small but analgesic concentrations of ether or cyclopropane to the nitrous oxide and oxygen mixture, using thiopentone for the induction alone. Diathermy could not, however, be safely used with these otherwise valid techniques.