A CLINICAL TRIAL OF PEMPIDINE IN THE TREATMENT OF HYPERTENSION*

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Ganglion-blocking agents are undoubtedly the most potent hypotensive drugs at present available, and extensive research is being directed to the discovery of similar compounds which would be safe if given orally and would have less side-effects. At the moment, however, it is difficult to imagine that any drug whose main action is blockage of all impulses at autonomic ganglia can fail to produce unwanted parasympathetic effects. Pempidine is the most recently introduced of these compounds, and so far only one account of its use in hypertension has been published, by Harrington, Kincaid-Smith and Milne,[1] who suggested that pempidine might hold certain advantages over mecamylamine in the treatment of hypertension. Mecamylamine, a secondary amine, has been more extensively used lately than the quaternary amine derivatives such as hexamethonium, pentolinium and chlorisondamine, mainly because mecamylamine, in being rapidly and completely absorbed from the gut,[2] made oral therapy more effective and predictable. However, mecamylamine also has certain disadvantages. Since its excretion is slow and irregular,[2] toxic effects from overdosage may be prolonged for days—even with danger to life.

Paralytic ileus is the most important and serious of these side-effects. Resultant vomiting and diarrhoea may cause a reduction of renal blood-flow with further delay in excretion of the drug, and prolongation of the toxic effects. Patients with mecamylamine ileus have, on occasion, been diagnosed by unsuspecting surgeons as cases of acute intestinal obstruction, and exposed to the danger of unnecessary laparotomy.[3]

In view of these disadvantages, a safer and more effective ganglion-blocking agent has been searched for. We were consequently glad to be able to study the new drug pempidine.† Experimental studies on animals[4] have shown that pempidine acts on the autonomic ganglia and that the drug was more active and less toxic than mecamylamine.

Chemistry and Pharmacology of Pempidine

Pempidine is a tertiary amine and a simple derivative of piperidine. Pempidine is 1 : 2 : 2 : 6 pentamethylpiperidine, and is available for oral use as the bitartrate salt; but the hydrochloride is preferred for intravenous use. The drug was originally designated M. & B. 4486, but it is now commonly known as pempidine (Perolysen May and Baker, or Tenormal I.C.I.).

No detailed pharmacological studies were undertaken in the present series of patients treated with pempidine. Such studies were made by Harrington *et al.*[1] on 32 hypertensives without renal failure and 2 hypertensives with renal failure. They also compared pempidine with mecamylamine. Their findings can be summarized as follows:

1. Like mecamylamine, pempidine is completely absorbed from the gastro-intestinal tract.
2. Both drugs are excreted by the kidneys, and elimination is delayed if there is renal failure.
3. The excretion of both mecamylamine and pempidine is influenced by variation of urinary pH, excretion being reduced by alkalization of the urine, and increased by acidification. However, urinary pH changes affect the excretion of pempidine to a lesser extent than mecamylamine, and pempidine is excreted more rapidly than mecamylamine no matter whether the urine is acid, alkaline or normal.
4. The distribution of both drugs in blood and tissues is much the same, but there is less tissue affinity for pempidine and, unlike mecamylamine, it is not significantly bound to plasma protein. This partly explains the more rapid excretion of pempidine, since a greater fraction of any given dose remains within the extracellular space, and is therefore available for excretion.
5. The minimum lethal dose of pempidine is considerably higher than that of mecamylamine.
6. Both drugs readily cross the blood-brain barrier, and are found in relatively high concentrations in the central nervous system. The pharmacological effects of lethal doses of pempidine in rats are similar to those described for mecamylamine,[2] and include tremor and convulsions.

Clinical Material

Ten patients were treated with pempidine, and the trial extended over a period of about 6 months, but only half of the patients reached the stage of receiving maintenance treatment with pempidine. These patients all had serious hypertension with secondary cardiovascular and retinal changes due to the hypertensive state. Patients were first seen and assessed at the hypertension clinic, and then admitted for further investigations and treatment. Investigations were as thorough and detailed as possible in order to exclude any aetiological condition which might be curable. In none of the 10 cases did we find such an underlying cause.

Of the 10 patients, 5 had malignant hypertension with papilloedema, of which 3 were cases of essential hypertension, 1 chronic nephritis, and 1 a unilateral pyelonephritic kidney. Nephrectomy was performed in the last-mentioned case in an attempt to cure the hypertension, but the hypertension persisted after the operation and a grade-4 retinopathy remained unchanged. The other 5 patients had severe essential hypertension.

There were 6 females and 4 males in the series; 6 were in the relatively young age-group of 30-45 years, while the patient with chronic nephritis and malignant hypertension was a child of 14 years. This child was the only case with a raised blood urea (60 mg. %) at the time treatment was started.

Two patients were in mild hypertensive cardiac failure, and only 2 had previously been treated for hypertension—both with mecamylamine, with an unsatisfactory result.

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During the initial period in hospital, while investigations were proceeding, all the patients were either sitting up in bed or in a chair alongside the bed, but no other activity was allowed at this stage. To allow for uniformity in the assessment of the drug, salt restriction was not enforced and a normal ward diet was allowed.

Once drug treatment had been started, the patient was encouraged to be up most of the day, and many helped the nurses in some of their minor ward duties. At night they slept in a semi-upright position. These measures allowed for the maximum benefit to be derived from the postural hypotensive effect common to all ganglion-blocking drugs.[5]

CLINICAL TRIAL OF PEMPIDINE

Oral Dosage

Single oral doses of 15 mg. of pempidine bitartrate (7·5 mg. of pempidine base) were given to 5 patients. A similar oral dose of mecamylamine was given to the other 5 hypertensive patients in order to compare the onset duration of action of the two drugs (Fig. 1).

After an oral dose of pempidine a hypotensive effect was usually observed within 1 hour, although in one patient the onset of action was delayed for 3 hours. The total duration of hypotensive action was 6-8 hours. The maximal effect was observed 3-5 hours after the dose, and at this stage most patients developed postural giddiness on standing up from a semi-recumbent position. The additional fall of blood pressure demonstrates the well-known postural hypotension which occurs after the administration of a ganglion-blocking

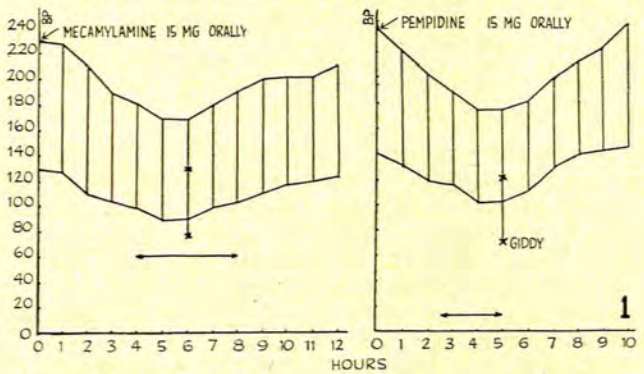

Fig. 1. Comparison of mecamylamine and pempidine given in similar oral doses in respect of onset and duration of action. Arrows indicate duration of postural hypotension and the additional fall of blood pressure on standing is also shown.

drug. The action of pempidine appears to be indistinguishable in this respect from that of mecamylamine and the other methonium compounds used in the treatment of hypertension. The relationship between the extent of the fall of blood pressure in the horizontal posture and the additional fall of blood pressure which occurs on standing varies from patient to patient. Some patients have a substantial fall of blood pressure in all postures with comparatively little postural hypotension. Others have very little fall in pressure when lying flat, but a considerable decrease in blood pressure on assumption of the erect posture.

After an oral dose of mecamylamine, a hypotensive effect was observed after about 2 hours. The total duration of hypotensive action was about 12 hours with the dosage used, although the maximal effect only lasted for 4-8 hours.

Comparing these two ganglion-blocking drugs, it can be seen that similar doses produced a similar hypotensive effect, but that the onset and duration of action is different. Pempidine acts within 1 hour but action only lasts for 6 hours, whereas mecamylamine acts within 2 hours and remains effective for 12 hours. Thus pempidine should be administered 4 times a day, while mecamylamine is usually administered twice a day, though sometimes a smaller or equal midday dose is necessary for optimum control of blood pressure.

With both drugs the resulting fall in blood pressure after a single oral dose was smooth and no undue fluctuation in pressure occurred.

After a single oral dose of 15 mg. one of the pempidine patients developed a severe reaction 6 hours after administration, viz. an acute gastro-intestinal upset with vomiting and diarrhoea, and a few hours later was noted to have some abdominal distension. Such an incident did not occur with any of the mecamylamine patients receiving a single large oral dose. This might suggest that pempidine is the more toxic of the two drugs when both drugs are employed at the same dosage.

Effect of Alteration in Urinary pH on Excretion of Pempidine

It has already been mentioned that Harrington *et al.*[1] showed that the renal clearance of both mecamylamine and pempidine is dependant upon urinary pH, the clearance being increased in an acid urine and decreased in an alkaline urine. Variation in excretion, however, was found to be less with pempidine, and it was stated that the hypotensive effect was therefore less likely to be influenced by changes in acid-base balance than with mecamylamine.[1]

A patient was first given 15 mg. of pempidine orally and showed the expected response as regards the onset and duration of action of pempidine. The patient was then given 12 g. of sodium bicarbonate daily for 2 days, which caused the urine to become alkaline. Another dose of pempidine was then given orally, and showed that a significant increase in the therapeutic action and side-effects of pempidine occurs when the urine is made alkaline. The duration of

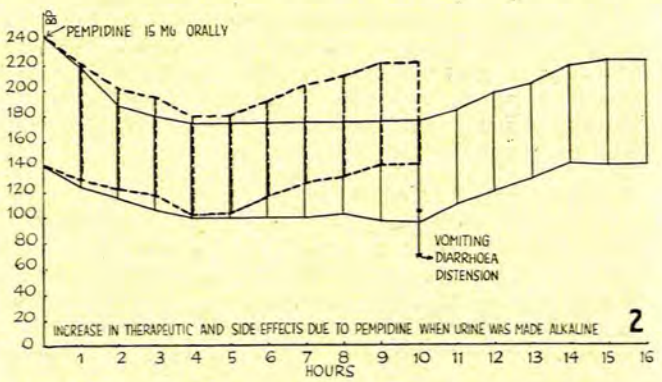

Fig. 2. Increase in therapeutic action and side-effects of pempidine when urine was made alkaline. The curve now resembles the onset and duration curve of mecamylamine. The dotted-line curve shows response to pempidine in the same patient before sodium bicarbonate was given to alkalize the urine.

action was now in the vicinity of 14 hours, and postural hypotension, vomiting and diarrhoea occurred 10 hours after administration. The curve (Fig. 2) closely resembles

the onset-duration curve of mecamylamine, which agrees with the findings of previous workers,[1] who compared the cumulative excretion of pempidine and mecamylamine over 24 hours, while varying the urinary pH. It was found that the lowest rate of excretion of pempidine in an alkaline urine was similar to the highest rate of excretion of mecamylamine in an acid urine.

Acidification of the urine by giving the patient ammonium chloride did not produce a striking alteration in the pempidine onset-duration curve. There was, however, a tendency to a diminished therapeutic effect from the drug, and this one would expect to find due to the more rapid excretion in an acid urine.

Continuous Oral Treatment

Only 10 patients have been observed on continuous treatment with pempidine. They were an unselected group, all of whom had serious hypertension as assessed from symptoms, blood pressure readings, retinal vessels, chest X-ray and electrocardiography. Pempidine was given 4 times during the day, the doses being spaced at 5-hourly intervals from 7 a.m. to 10 p.m. On this regime a sustained reduction in blood pressure may be obtained throughout the day. In some cases the last dose at night was doubled in order to give a prolonged action during the night hours. In one patient with impaired renal function the drug was only given 3 times a day.

Duration of Treatment

Of the 10 patients in the pempidine series, only 5 were eventually discharged from hospital on pempidine, and these were well controlled when they left. In these patients treatment is being continued up to the present time for a period varying from 8 weeks to 20 weeks. Of the remaining 5, one died 3 days after starting pempidine, and treatment had to be stopped in the 4 others because of the severity of side-effects.

Dosage

The dosage of pempidine required to produce an adequate hypotensive effect varied widely, in our series from 10 mg. to 60 mg. daily. The average total daily dose given as maintenance treatment in this series was 40 mg. of the bitartrate. In Harrington's series[1] the corresponding average total daily dose was 32·5 mg.

In our series treatment was usually started with a dose of 2·5 mg. 4 times a day, and raised rapidly by increasing each dose by 2·5 mg. daily until a satisfactory reduction in blood pressure was achieved or the development of toxic effects hampered further progress. Once serious toxic effects occurred, the drug was stopped until the serious symptoms ceased, and then the administration was resumed at a dosage reduced to that previously found to be safe. On this safe dosage, increments were now made with 2·5 mg. of pempidine *per day*. In this way we were able to control at least 3 patients who would have been failures in the trial if the recommended dosage increment of 2·5 mg. *per dose* had been adhered to.[1]

From this experience it appears that the therapeutic and toxic doses of pempidine lie close to each other. We have for instance, found on a few occasions that a dose of say 40 mg. daily produced adequate control of blood pressure, but with severe and limiting side-effects; when the dose was reduced to 37·5 mg. daily, the drug was tolerable yet still therapeutically effective. It is possible that had we tried this dosage scheme earlier on, we might have had more success with pempidine.

Harrington *et al.*[1] did not mention this difficulty in their trial of pempidine. They increased each dose with 2·5 mg. daily until a satisfactory reduction in blood pressure was achieved, and found it possible to reach a stable therapeutic dose level with reasonable safety within a few days.

Tolerance

No evidence has been seen of the development of tolerance to pempidine, analogous to that seen with hexamethonium and other quaternary ammonium compounds.[6] In this respect the drug resembles mecamylamine.

Combination with Other Drugs

In 2 cases reserpine, and in 1 case chlorothiazide, was added to the pempidine. This was done to try and reduce the side-effects of pempidine, and in all 3 cases the combination allowed more successful treatment, suggesting that these compounds potentiate the action of pempidine as has been described with other hypotensive agents.[5]

Side-effects

Side-effects (Table I) occurred with disappointing frequency. Only one of the 10 patients treated with pempidine did not experience troublesome side-effects, and this patient was fortunate enough to have her blood pressure controlled on a very low dosage, viz. 10 mg. per day. Pempidine had to be abandoned in 5 cases because of the severity of side-effects.

TABLE I. SIDE-EFFECTS OF PEMPIDINE (10 PATIENTS)

Alimentary	
Dry mouth	8
Bitter taste	2
Nausea and vomiting	7
Constipation	8
Distention	7
Severe ileus	2
Diarrhoea	3
Urinary	
Difficulty in micturition	2
Retention	1
Visual	
Blurring of vision	3
CNS	
Tremors	2

One of these patients subsequently died, but those remaining have all been successfully controlled with mecamylamine. Of the 5 patients successfully controlled with pempidine, 3 required laxatives regularly to avoid constipation and, of these 3, one also required pilocarpine eye drops for blurred vision, and another neostigmine to relieve the feeling of fullness and distension which accompanied the constipation.

From the list of side-effects (Table I) it will be seen that the most troublesome ones are from the gastro-intestinal tract, and the severity of these were responsible for cessation of therapy in one-half of the patients in this small series. A true ileus with constipation, continuous vomiting and absence of bowel sounds occurred in 2 patients; this must be regarded as a very serious complication.

Retention of urine occurred in one patient, a male of 60 years with malignant hypertension, and pempidine had to be stopped. This patient had previously failed to have his blood pressure controlled on mecamylamine for the same reason. He had a transurethral resection for bladder-neck stenosis, and subsequently we managed to control his blood pressure reasonably well on pempidine.

Our pempidine trial came to an abrupt end when one patient died as a result of a severe ileus, which must be attributed to the drug.

This patient was an African male aged 60 years with severe essential hypertension. He presented with headaches and progressively increasing effort dyspnoea over the previous 2 years. He also had a chronic cough with mucopurulent sputum, and suffered from osteo-arthritis. Blood pressure 250/140 mm. Hg. His heart was enlarged, with a left ventricular type of apex beat, but he was not in cardiac failure. A grade-2 hypertensive retinopathy was found. Routine special investigations did not reveal anything of note. The blood urea was normal.

Penicillin and streptomycin were given for his mucopurulent bronchitis, and syrup of codeine phosphate 6-hourly for the irritating cough. He was started on 2·5 mg. of pempidine 4 times a day on 12 November 1958. Ambulation was encouraged. He was quite well on 13 November, but had no bowel action that day. His blood pressure, taken 4 times a day, averaged 220/120. Agarol was prescribed for constipation, and the next morning, 14 November, 2 days after starting pempidine, he complained of abdominal distension as well as constipation; his abdomen was found to be distended, but bowel sounds could be heard. The blood pressure was then 200/120. His urine was strongly acid. The pempidine was stopped, and the patient was given carbachol, 0·5 mg. intramuscularly. That same afternoon he started vomiting. Abdominal distension had increased, and no bowel sounds could be heard. The blood pressure was now 170/100. The urinary output was satisfactory and the urine was still acid.

Intravenous drip and gastric suction were now started, and the patient was catheterized and continuous bladder drainage instituted. At first he seemed to improve, but during that night he developed severe diarrhoea. When seen on 15 November he appeared to be in a shocked state; pulse 120 p.m., blood pressure 140/100, cold and sweating. The urinary output was 1 litre and the gastric suction 1½ litres during the previous 24 hours. The serum electrolytes estimated at this stage were normal, except for a rather low serum-potassium (3·5 mEq. per litre), despite which the electrocardiogram, except for a tachycardia, was not significantly different from that taken on admission.

The patient received 1½ litres of Darrow's solution, 1 litre of sodium chloride and 2 litres of dextrose water, plus 2 g. of potassium chloride, over the next 24 hours. His condition did not improve, and finally solucortef was also given intravenously *via* the drip.

The blood pressure never fell below 140/100 and urinary output remained satisfactory throughout this period. The patient died later that night (15 November).

At autopsy the pathological diagnosis was paralytic ileus with meteorism, dilatation and early peritonitis of the small intestine. Purulent bronchitis and bronchopneumonia were present in both lungs, the heart showed left ventricular hypertrophy and the kidneys slight nephrosclerosis. An unexpected finding was the presence of numerous amoebic ulcers in the caecum, ascending colon and transverse colon. The patient had never mentioned to us any complaint referable to this.

As a result of this tragic death it was decided to end the clinical trial of pempidine, and we have, temporarily at least, abandoned further use of the drug in the treatment of hypertension. It was interesting to find a recent report[7] of a patient who died of severe diarrhoea after mecamylamine treatment. At necropsy gross ulceration of the colon was present, and this was thought to be due to a direct local effect of the drug. In our patient, however, the treatment was not the cause of the ulcers, for amoebae were seen microscopically.

Results in Cases treated with Pempidine

In 5 patients we obtained a satisfactory control of blood pressure with pempidine as the major drug used in treatment (Table II). Parallel with a fall in blood pressure, there was a general improvement in these patients. Headaches due to hypertensive treatment disappeared and the patient with cardiac failure developed a better exercise tolerance and could dispense with the digitalis and diuretics which he required before this treatment. Of these 5 patients 3 were cases of malignant hypertension, which was successfully treated with pempidine. In all 3, papilloedema disappeared after an average treatment period of 6 weeks.

TABLE II. RESULTS IN 5 PEMPIDINE-TREATED CASES

Average BP (mm. Hg)		*Retina*	*Dose*	*Side-effects*
Before	*After*	*(Keith-Wagener)*	*(mg. per day)*	
260/170	200/120	IV→III	30	Dry mouth Constipation Vomiting Blurred vision.
240/140	160/105	II→II	20	Constipation Dry mouth Bitter taste.
230/130	170/110	II→II	10	—
260/150	180/120	IV→II	60	Severe visual disturbances.
280/160	180/100	IV→II	37·5	Dry mouth Constipation.

Side-effects were troublesome in 3 of the 5 patients and they required additional specific treatment for constipation, dry mouth, blurred vision and a feeling of abdominal distension.

DISCUSSION

Harrington *et al.*[1] also report a syndrome of early paralytic ileus, with vomiting, abdominal pain and distension in 3 out of 27 patients treated with pempidine. In their cases the symptoms cleared completely within 12 hours of stopping the drug. We were less fortunate with this one patient who died, although our other patient who developed ileus recovered fairly rapidly, but even here intravenous therapy and gastric suction were necessary. The only side-effects occuring frequently in Harrington's series of 27 patients,[1] were constipation (66%), dryness of the mouth (66%) and blurring of vision (45%). The complaints were regarded as major in only 3 cases.

In our experience toxic symptoms with pempidine occur early, usually on the same day as the toxic dose is instituted, but in 2 cases side-effects were delayed for 2 days. Parallel with this, a fall of blood pressure has always occurred and in most cases to a satisfactory level from a therapeutic point of view. If the same dosage that produced toxicity originally was given again 1 month later, the same side-effects occurred, showing that no significant tolerance to pempidine developed.

We have also found that there was only a narrow margin between the toxic and therapeutic doses of pempidine. Patients fairly comfortably stabilized on a certain dosage, regularly developed more serious toxic symptoms, such as distension and vomiting, on a dosage increment of as little as 2·5 mg. per day.

Comparison with Mecamylamine

Harrington *et al.*[1] concluded from their study of pempidine that there was little to choose between this drug and mecamylamine in respect of their side-effects. We have, however, been far less successful with pempidine than with mecamylamine. Our 4 pempidine failures were all controlled and discharged on mecamylamine. We had the opportunity of trying only 2 mecamylamine failures on pempidine, and it was unsuccessful and had to be abandoned in both.

If we compare our last 20 patients treated on mecamylamine, we find that control was easier and there were

less interruptions caused by stopping and starting the drug. Consequently the average stay in hospital was shorter.

Side-effects also occurred with mecamylamine, but they were less frequent and less serious. Constipation and dry mouth occurred in less than half of our mecamylamine patients, but in 8 out of 10 of the pempidine series. A true ileus occurred in 2 of our pempidine patients, but in none of the 20 mecamylamine-treated group, although it is a recognized danger with mecamylamine.

SUMMARY AND CONCLUSIONS

Pempidine has been used as a hypotensive agent in 10 patients with severe hypertension. Though the series is small, we have been able to form certain impressions about the drug. Pempidine given by mouth undoubtedly lowers the blood pressure in most patients, by virtue of its ganglion-blocking effect, but it would be wrong to assume that it is an ideal drug for the treatment of hypertension.

Pempidine has many points of similarity to mecamylamine. Both are freely absorbed from the gut, as a result of which a constant therapeutic effect from day to day can be obtained with oral administration. Both are excreted more rapidly in an acid than in an alkaline urine, and both easily cross the blood-brain barrier.[1]

Pharmacologically pempidine has certain advantages over mecamylamine which should make it a potentially more useful drug. It is more rapidly excreted, chiefly because of a lower tissue affinity for the drug, and excretion of pempidine is less affected by variation in acid balance than that of mecamylamine. These pharmacological advantages we have found of relatively little account in practice, and severe side-effects, the main drawback with all ganglion-blocking agents, occur with disappointing frequency. We have found them to occur rather more frequently with pempidine than with mecamylamine, and certainly the gastro-intestinal side-effects from pempidine seem to be more serious.

After losing one patient from a pempidine ileus, we have abandoned further use of the drug in the treatment of hypertension. At the moment we do not feel that it can replace mecamylamine or pentolinium as probably the most useful drugs for the long-term treatment of severe hypertension.

Pempidine might well be held in reserve. Good control over blood pressure can be obtained with it in those patients who are fortunate enough to be able to tolerate it, and since responses to ganglion-blocking drugs are highly individual, it is likely that some patients may be more comfortable on the one drug than the other, whether this be mecamylamine, pentolinium, chlorisondamine or pempidine.

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REFERENCES

1. Harrington, M., Kincaid-Smith, P. and Milne, M. D. (1958): Lancet, **2**, 6.
2. Milne, M. D., Rowe, G. G., Somers, K., Muehrcke, R. C. and Crawford, M. A. (1957): Clin. Sci., **16**, 599.
3. Grant, A. P. and Boyd, J. S. (1957): Lancet, **1**, 713.
4. Spinks, A. and Young, E. H. P. (1958): Nature (Lond.), **181**, 1397.
5. Smirk, F. H. (1957): *High Arterial Pressure*. Oxford: Blackwell Scientific Publications.
6. Smirk, F. H. and Alstad, K. S. (1951): Brit. Med. J., **1**, 1217.
7. Barnett, A. J. (1958): Lancet, **1**, 49.
8. Wagener, H. P. and Keith, N. M. (1939): Medicine (Baltimore), **18**, 317.