Injection treatment immediately put an immobilized patient on his feet with no disability. A few cases like this and one is so sold on the treatment that restraint must be used or the proper indications will be disregarded.

About the knee, my results have not been good. This may be due to my own persistent difficulty in assessing cartilage and cruciate injuries. I inject no more knees and would counsel similar caution to others in treating this area.

Evidence of osteoarthritis in the back—present perhaps asymptptomatically for years—makes one pause in assessment of the case of so-called “myositis” or “fibrositis” or “lumbago” or “acute back strain.” If passive movement through a complete range is painless—and this is very difficult to assess—and all the indicated criteria are present, the treatment should be attempted. No harm is done and the possible end results justify the occasional failures.

SUMMARY

1. An attempt has been made to revive interest in an old but often neglected part of our armamentarium.
2. Definite criteria before its use are laid down.
3. The procedure is outlined step by step.
4. A possible physiological explanation is postulated.

PHENURONE AND HEPATITIS*

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The modern medical treatment of the epilepsies involves the use of a number of relatively new drugs, the toxic effects of some of which are not yet clearly defined.

Tridione, of particular value in petit mal and myoclonic epilepsy, has been found to produce neutropenia and agranulocytosis, glare phenomenon with photophobia, and drowsiness or lethargy, and in rare instances, nephrosis. Davis and Lennox found paradione, which is closely related to tridione, to be associated with much less photophobia, and considerably less severe neutropenia than was tridione, when compared in similar patients, although paradione was slightly less effective. Mesantoin has been reported as leading to drowsiness, skin rashes and neutropenia, and acute aplastic anemia was observed by England and McEachern during mesantoin therapy.

Phenurone (phenacetylurea), one of the most recent arrivals in the field (introduced by Abbott Laboratories), appears also to have its specific disadvantages. Its chemical structure is related to that of dilantin and mesantoin; if the hydantoin ring is opened at a certain nitrogen-carbon linkage, the corresponding acetylyurea is formed. Gibbs, Everett and Richards’ found it to be particularly useful in the control of psychomotor seizures, which are relatively poorly controlled by other medication. However, as they report, it not infrequently exaggerates previously existing personality disturbances. The result may resemble hysteria, schizophrenia, or psychopathic states, representing a wide variation, but in any one patient the abnormality may be fairly constant. Phenurone may also produce anorexia and nausea, feelings of weakness, headache, insomnia, palpitation and rash, listed in order of decreasing frequency.

In view of the possible wide usefulness of phenurone and the necessity of assessing its toxic reactions, it was considered that the following case history, in which jaundice occurred in a patient who had been treated with the drug, would be of interest. Liver function tests were recorded. In this case, epileptic attacks had developed in adult life secondary to cerebral tumour.

CASE HISTORY

The patient, a well-nourished, white male, aged 42, was admitted to the Montreal Neurological Institute on August 17, 1949. He had been in good health until February, 1946, when he had begun to suffer from brief minor epileptic attacks consisting of simple rigid standing and staring, at first momentary, and later lasting five to ten seconds, of frequency about twice monthly and continuing over the ensuing years to the time of admission. In addition, he had had a major attack on at least three occasions over the past 3 years, consisting of falling, unconsciousness, and on one occasion tongue-biting.

Detailed description of the major attacks was as follows: Aura.—Subjective sensation of unsteadiness. Pattern of attack.—Generalized tonic spasm with falling, and unconsciousness lasting one to two minutes, and followed, on one or two occasions, by confusion, and once by automatism, during which he fought off persons who tried to assist him. Post-ictal period.—Amenesia for the entire attack. No evidence of aphasia, but following attack, speech became thick and mumbling.

About November 1948, after dilantin and phenobarbital had failed to control his attacks, he was placed on a regimen of mesantoin and phenobarbital (details of dosage not available). Several weeks later, the pa-
tient became ill with lethargy, general malaise, temperature of 101° F. and a faint rash. He was attended by several physicians, who excluded the common causes of fever of unknown origin. His temperature continued elevated between 100 and 103°, the rash becoming a generalized macular erythematous eruption. The anti-convulsant medication was suspected, and following cessation of the drugs the fever and rash quickly subsided.

In the last several months prior to admission, the patient had shown failing memory for recent events, and inability to concentrate, decreasing energy and drive, with increasing drowsiness. From the above description, it is evident that some of his seizures were suggestive of psychomotor attacks, and accordingly because of their persistence, two months prior to admission his medication was changed to phenurone 0.5 gm., three times daily, with phenobarbital 5/4 gr., four times daily. In the last two weeks, because it appeared to be ineffective, the phenurone had been reduced by the patient and his relatives to 0.5 gm. once daily, and it was stopped entirely following the first consultation here on August 14, 1949.

During the last few weeks before admission, the patient had noticed slight dragging of his left leg periodically. His wife had noticed that he had a slurred

**Table I.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal value</th>
<th>Patient: August 18</th>
<th>Patient: August 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total serum proteins</td>
<td>6.9 to 8.5 gm. %</td>
<td>7.04 gm. %</td>
<td></td>
</tr>
<tr>
<td>Albumen</td>
<td>4.4 to 6.0 gm. %</td>
<td>4.35 gm. %</td>
<td></td>
</tr>
<tr>
<td>Globulin</td>
<td>1.5 to 3.0 gm. %</td>
<td>2.69 gm. %</td>
<td></td>
</tr>
<tr>
<td>Bilirubin—direct</td>
<td>0.1 to 0.8 mgm. %</td>
<td>3.1 mgm. %</td>
<td>1.45 mgm. %</td>
</tr>
<tr>
<td>total</td>
<td>0.1 to 0.8 mgm. %</td>
<td>4.4 mgm. %</td>
<td>2.00 mgm. %</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>3 to 13 units (King-Armstrong)</td>
<td>12.9 units</td>
<td></td>
</tr>
<tr>
<td>Cephalin cholesterol flocculation</td>
<td>0 to 1+</td>
<td>4+</td>
<td>negative</td>
</tr>
<tr>
<td>Thymol turbidity</td>
<td>0 to 4 units</td>
<td>6.35 units</td>
<td></td>
</tr>
<tr>
<td>Thymol flocculation</td>
<td>0 to 1+</td>
<td>trace</td>
<td>negative</td>
</tr>
</tbody>
</table>

complexion. On two occasions in the last 10 days the patient had been incontinent of urine during sleep.

**General physical examination.**—(1) Sclera obviously icteric. Slight yellowish tinge to skin of abdomen. (2) Liver edge palpable two finger-breaths below the right costal margin, smooth in outline, of soft consistency and not tender. No other abdominal masses or tenderness.

**Neurological examination.**—(1) Difficulty in concentration. (2) Speech slow and hesitant, but not frankly dysarthric or aphasic. (3) Optic fundi showed questionable blurring and elevation of nasal margins of both optic discs. (4) Plotting of visual fields both by perimeter and on Bjerrum screen showed a small left homonymous upper field defect. (5) Slight weakness and slowness of voluntary movement of the lower face. (6) Slight increase in deep tendon reflexes on the left side (left biceps, patellar and ankle jerks). (7) Gait showed a slight tendency to drag the left foot and to swing the left arm less than the right arm. A clinical diagnosis of a right temporal neoplasm was made. This was supported by the results of ventriculography. At operation, a neoplasm was found involving almost the whole of the left temporal lobe, extending to the margins of the parietal and the occipital lobes. A removal was carried out, the histological sections showing the appearance of a piloid astrocytoma. The patient made an uneventful recovery from the operation, was discharged home on September 8, 1949, and has remained free of attacks to the date of this report (four months). The jaundice had disappeared clinically by August 27.

**Discussion**

In summary, a patient with focal cerebral seizures was treated for two months with phenurone and phenobarbital, at the end of which time he showed jaundice, which rapidly cleared following withdrawal of the phenurone, so that about ten days later the jaundice was not clinically appreciable. The liver edge was no longer palpable. There had been no previous attacks of jaundice. Infectious hepatitis is difficult to exclude, but there were no known other instances of jaundice in the family or in the community where the patient had been living, and the patient had received no intravenous injections or blood transfusions in the past year. Hepatic cirrhosis is unlikely from the negative past history, and the findings of the liver function tests.

There was no evidence of intra-abdominal neoplasm. The strongest indication that jaundice was due to a drug intoxication was its prompt disappearance when the drug was withdrawn. Further support is given to this explanation by the results of the liver function tests (Table I), which show evidence of parenchymal liver cell damage (cephalin cholesterol flocculation and thymol turbidity tests), but no evidence of an obstructive element (normal alkaline phosphatase), and no evidence of long-standing liver disease (as judged by the plasma proteins). Flocculation and turbidity tests returned to normal within four days, and the serum bilirubin had markedly subsided. Urine tests for bile (modified Gmelin's test) gave a faintly positive result on August 18, and showed only a trace on August 22.

Since this patient had had a previous toxic reaction to mesantoin, the possibility that he
presented an unusual degree of intolerance or an idiosyncrasy in relation to these drugs cannot be definitely excluded. Recently, however, another epileptic patient has been observed here who stated that a rather severe bout of jaundice had followed phenurone medication. Other drugs had been taken simultaneously and details are not available. Further, Davidson and Lennox* recently surveyed a series of over 100 cases of epilepsy treated with phenurone, and in one of their cases, liver damage was observed. They found phenurone had advantages over other medication, but noted the occurrence of side effects such as skin rashes, gastric disturbances, and personality disorders.† Gibbs et al.§ also noted jaundice in one case of their series treated with phenurone, which subsided when the drug was stopped and reappeared when it was given again.

Experimental work at Abbott Laboratories as reported by Everett10 indicated that in animals the liver plays some part in the destruction of phenurone. In view of this, although jaundice was not produced in animals with large dosages over long periods, the occurrence of jaundice clinically in a small percentage of cases, might not be surprising. This toxic effect of phenurone (phenacetylurea) may be related to the fact that in experimental animals, and probably in man, the liver is the site of production of urea.

Apparently then, it would be well to supervise patients taking phenurone by requiring them to report frequently during the first few months, for clinical examination and urinalysis. Before using phenurone, enquiry should be made to exclude a history of past liver disease (as well as of previous mental disorders).

**SUMMARY**

1. A case history is presented in which an epileptic patient having been treated with phenurone was found to have jaundice, which promptly subsided following withdrawal of the drug.

2. Liver function tests indicated that the jaundice was due to hepatitis presumably of toxic origin. There was no evidence for other common causes of jaundice.

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*Abbott Laboratories, before making phenurone generally available, has carefully gathered results of extensive clinical trials, and report† that in the first 1,000 cases of patients treated with phenurone, on which data are available, some degree of liver dysfunction has occurred in about 5% of cases. Phenurone is still under investigation and is not yet available on the market.

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† Read before the Eightieth Annual Meeting of the Canadian Medical Association, Section of Pediatrics, Saskatoon, June 16, 1949.