The Electrophysiological Properties of Diphenylhydantoin Sodium as Compared to Procaine Amide in the Normal and Digitalis-Intoxicated Heart

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SUMMARY
The effects of diphenylhydantoin sodium (Dilantin) on ventricular automaticity, intraventricular conduction, atrioventricular (A-V) conduction, and sinus rate have been determined in the digitalis-intoxicated and normal heart. These effects have been compared with procaine amide. Diphenylhydantoin sodium depresses ventricular automaticity and enhances A-V conduction while having little or no effect on intraventricular conduction or sinus rate. Procaine amide differed from diphenylhydantoin sodium in that it caused depression of both A-V and the intraventricular conduction, as well as slowing of the sinus rate.

The results indicate that the electrophysiological properties of diphenylhydantoin sodium make it superior to procaine amide in the treatment of digitalis toxicity. Both diphenylhydantoin sodium and procaine amide can suppress digitalis arrhythmias due to enhanced automaticity, but procaine amide may promote "re-entry" arrhythmias by potentiating the intraventricular conduction defect caused by the glycoside. In addition, diphenylhydantoin sodium appears to antagonize the action of digitalis on the A-V node, while procaine amide increases the digitalis-induced A-V block. It is concluded that the electrophysiological properties of diphenylhydantoin sodium make it an excellent agent in treating digitalis-induced arrhythmias.

Additional Indexing Words:
Intraventricular conduction A-V conduction Re-entry arrhythmias
Acetylstrophanthidin

DIPHENYLHYDANTION sodium (Dilantin) has been found in several clinical and experimental studies to be a useful drug in the treatment of cardiac arrhythmias.\textsuperscript{1-7} It has been particularly effective in arrhythmias induced by digitalis toxicity.\textsuperscript{4-7} However, although the use of diphenylhydantoin sodium as a cardiac anti-arrhythmic agent is now widespread, little is known about its mechanism of action in the normal or arrhythmic heart.

The object of the present study was to determine the electrophysiological effects of diphenylhydantoin sodium that account for its mechanism of action as an anti-arrhythmic agent in the treatment of digitalis toxicity. Determinations were made of the effect of diphenylhydantoin sodium on ventricular automaticity and intraventricular conduction as well as on A-V conduction and sinus rate in the digitalis-intoxicated and normal heart. The actions of diphenylhydantoin sodium were compared with those of procaine amide (Pronestyl) under similar circumstances.

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Methods

Adult mongrel dogs, weighing 10 to 20 kg, were anesthetized with sodium pentobarbital, 30 mg/kg intravenously. The trachea was cannulated, and artificial ventilation was maintained with a Harvard* respirator pump. A polyethylene catheter was inserted into the femoral artery and attached to a Statham pressure transducer for continuous monitoring of arterial pressure. The femoral vein was then cannulated for the infusion of drugs. A standard lead II electrocardiogram was recorded throughout the experiment.

The right fourth intercostal space was incised and the right atrium and the basal portions of the right ventricle were exposed through a wide pericardial opening. Employing a technique described elsewhere,* electrograms of the bundle of His were obtained by the insertion of two fine, Teflon-coated, stainless steel wires into the region of the bundle of His. The wires were inserted through the intact atrial wall with no discernible electrophysiological or hemodynamic effect. In addition, the Teflon-coated wires permitted controlled ventricular pacing from the region of the bundle of His resulting in normal sequential activation of the ventricles. Pacing stimuli were delivered to the bundle of His from an AEI† laboratory stimulator through a stimulus isolation unit. The right cervical vagus nerve was sectioned, and stimulating electrodes were applied to its distal end. All records were registered on a multitrace oscillographic recorder.

Intraventricular conduction was measured as the interval between the electrogram of the bundle of His and the end of the QRS complex. A-V conduction was taken as the interval between the beginning of the P wave and the spike of the bundle of His. Records of intraventricular and A-V conduction were taken at a paper speed of 200 mm/sec. In order to unmask any underlying intraventricular conduction defects, the heart was paced by stimulation of the bundle of His at rates between 180 to 240/min at appropriate times throughout the procedure. The interval between the stimulus artifact and the end of the QRS during pacing from the bundle of His could be compared at different paced rates to the bundle of His-QRS interval measured during sinus rhythm. Ventricular automaticity was determined as the time for a ventricular escape beat to terminate the cardiac arrest produced by the stimulation of the distal end of the sectioned right vagus nerve.9 The stimuli were applied at a frequency of 20/sec; the duration of each impulse was 2.5 msec. The ventricular escape time (VET) was determined during three separate control runs and was found to be reproducible for each animal within 2 to 3 seconds. The configuration and spontaneous rates of the complexes during ventricular escape were also consistent.

After control records were taken, digitalis intoxication was produced in 15 dogs over a period of 20 to 60 minutes by a single intravenous injection of 7.5 μg/kg of acetylstrophanthidin* followed by continuous infusion of the drug at a rate of 2.0 to 3.0 μg/kg/min. Ventricular automaticity and conduction times during sinus rhythm (RSR) and pacing from the bundle of His were determined at intervals of 2 to 5 minutes throughout the entire experiment. With the appearance of a stable unifocal or multifocal ventricular tachycardia, diphenylhydantoin sodium or procaine amide was administered to convert the arrhythmia to regular sinus rhythm. In 10 dogs, diphenylhydantoin sodium was given in a dose of 5 mg/kg intravenously over a period of 30 seconds. In all instances, there was conversion to regular sinus rhythm. Procaine amide was given as a single intravenous injection in three dogs. Using the conversion to sinus rhythm as an end point, the dose of procaine amide required was 30 mg/kg. In two dogs, procaine amide was titrated in separate injections of 10 mg/kg over a period of 4 minutes, with an interval between doses of 10 to 20 minutes. The latter regimen was used to simulate the clinical administration of procaine amide. In one instance, conversion to regular sinus rhythm was produced with injection of 15 mg/kg of procaine amide, while in the other dog the total dose of 30 mg/kg did not revert the ventricular rhythm (see discussion).

In four additional dogs, the effects of diphenylhydantoin sodium (5 mg/kg) alone on ventricular automaticity, A-V and intraventricular conduction, as well as sinus rate were recorded. The effects of procaine amide alone on these properties were also determined in two separate experiments.

Results

Effects of Diphenylhydantoin Sodium on the Digitalis-Intoxicated Heart

During the infusion of acetylstrophanthidin, the ventricular escape time (VET) was progressively shortened. Immediately prior to the development of digitalis toxicity, a different and faster ventricular focus was unmasked

*Harvard Apparatus, Dover, Massachusetts.

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by stimulating the vagus nerve. It was this new ventricular focus that eventually increased in rate until it dominated the sinus rate and established an overt ventricular tachycardia. Acetylstrophanthidin usually produced no discernible change in intraventricular conduction paths; however, with pacing from the bundle of His, prolongation of the intraventricular conduction time was almost always seen (table 1). The well-known effect of acetylstrophanthidin on A-V conduction was invariably seen, that is varying amounts of first and second-degree block.

Upon administration of diphenylhydantoin sodium (5 mg/kg), the ventricular tachycardia was always converted to regular sinus rhythm within 30 to 45 seconds, although occasionally an additional 5 mg/kg of diphenylhydantoin sodium was required to maintain the rhythm once regular sinus rhythm was restored. Following conversion to regular sinus rhythm by diphenylhydantoin, VET was prolonged beyond control values and the ventricular escape complex showed the same configuration as the control escape focus (fig. 1). In contrast to the pronounced depressant effect on ventricular automaticity, diphenylhydantoin sodium only minimally and transiently slowed intraventricular conduction in two studies whereas, in six experiments, there was no measurable effect on intraventricular conduction time. In the two former studies, intraventricular conduction time was increased by less than 4.8% of control values and this effect persisted for less than 5 minutes. Pacing the heart from the bundle of His did not produce any significant increase in intraventricular conduction time, nor was any QRS aberration produced at the pacing rates employed (fig. 2).

Diphenylhydantoin sodium's effect on A-V conduction was determined in seven studies. In six of these, diphenylhydantoin sodium reversed the digitalis-induced prolongation of A-V conduction time within 2 minutes (fig. 3). In one study, a return toward normal

### Table 1

**Comparative Effects of Diphenylhydantoin Sodium and Procaine Amide on the Digitalis-Intoxicated Heart**

<table>
<thead>
<tr>
<th>No.</th>
<th>SR</th>
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<th>240</th>
<th>VET</th>
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<th>180</th>
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<td>92</td>
<td>61</td>
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| II. Procaine amide conversion of acetylstrophanthidin toxicity | | | | | | | | | | | | |
| 11  | 150 | 55  | 64  | —   | —   | —   | 160| 65  | 67  | —   | —   | 0   |
| 12  | 180 | 70  | 80  | 83  | 83  | 7   | 180| 87  | 80  | 83  | 85  | 0   |
| 13  | 140 | 78  | 79  | 81  | 81  | 40  | 140| 95  | 82  | 82  | 87  | 0   |
| 14  | 125 | 59  | 73  | 73  | 84  | 6   | 120| —   | 85  | 70  | —   | 0   |
| 15  | 150 | 52  | 78  | 78  | 78  | 6   | 150| 71  | 80  | 78  | 78  | 0   |

**Abbreviations:** SR = sinus rate; AVC = atrioventricular conduction time (msec); RSR = regular sinus rhythm; IVC = intraventricular conduction time (msec); 180 = bundle of His pacing at 180/min; 240 = bundle of His pacing at 240/min; and VET = ventricular escape time (sec).

*2* A-V block.

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PROPERTIES OF DIPHENYLHYDANTOIN SODIUM

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<td>ventricular rhythm</td>
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<td>135 98 93 93 100</td>
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</table>

Figure 1

The effect of diphenylhydantoin sodium on ventricular automaticity. (Top trace in A, B, and C) Lead II of the electrocardiograms; (bottom trace) electrograms of bundle of His (H.B.E.). (A) Control. Right vagal nerve stimulation (↓) produced a cardiac asystole for 9 sec before an escape beat occurred. (B) With the onset of digitalis toxicity vagal stimulation (↓) unmasks an immediate ventricular tachycardia. Note the differences in these complexes compared to the ventricular escape complex seen in A. On cessation of vagal stimulation (↑) regular sinus rhythm appears with intermittent ectopic complexes and fusion beats. (C) After restoration of regular sinus rhythm with diphenylhydantoin sodium (DPH), ventricular escape time with vagal stimulation occurs after 31 sec. Note that the ventricular escape complex is upright.

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was seen in 5 minutes. Diphenylhydantoin sodium appeared to have no effect on sinus rate (table 1).

**Effects of Procaine Amide on the Digitalis-Intoxicated Heart**

Procaine amide was found to have effects that differed from diphenylhydantoin sodium in these studies. In four of the five cases, procaine amide converted the digitalis-induced ventricular tachycardia to regular sinus rhythm. Ventricular escape time could not be accurately determined using vagal stimulation, probably because procaine amide is known to antagonize the effects of acetylcholine. However, in one study (table 1, II-15) the time for an escape beat to occur was prolonged beyond control values although the escape beat appeared to originate from the sinus node.

With the doses necessary for the conversion to regular sinus rhythm, procaine amide caused a marked increase of 26 to 87% in intraventricular conduction time which persisted for more than 2 hours. In contrast to diphenylhydantoin sodium, procaine amide consistently potentiated the A-V block produced by acetylstrophanthidin (fig. 3). Post-conversion sinus rates with procaine amide were always decreased below control values. After conversion of digitalis toxicity with procaine amide, stimulation of the bundle of His caused a marked prolongation of intraventricular conduction of 113 to 138% with QRS aberration. In one animal, the bundle of His was paced at a rate equal to the control

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**Figure 2**

The effect of acetylstrophanthidin and diphenylhydantoin sodium on intraventricular conduction. (Top traces in A, B, and C) Lead II of the electrocardiograms; (bottom trace) electrograms of bundle of His (H.B.E.). (A) Control. Note the bundle of His deflection (arrows) during the P-R interval of lead II. Pacing from the site of the bundle of His at 200 and 240/min (HP = 200, and HP = 240) produced the same QRS complex as seen during RSR. At both paced rates, the pacing impulse (p.i.) to S-wave intervals (76 msec) is essentially identical to the bundle of His to S-wave interval (75 msec) seen during RSR at a rate of 180 per minute. (B) During ventricular tachycardia (190/min) produced by acetylstrophanthidin, pacing from the bundle of His produced a slight increase in intraventricular conduction time (77 msec at 200 and 79 msec at 240/min). (C) Restoration of RSR with diphenylhydantoin sodium (5 mg/kg) again shows bundle of His activity; bundle of His pacing produced no significant change in intraventricular conduction from the control (77 msec during RSR, 77 msec at 180, and 80 msec at 240/min). Stimulus artifacts have been retouched for visibility.
sinus rate and showed a 56% increase in intraventricular conduction time over control values (fig. 4).

In another experiment the administration of 10 mg/kg of procaine amide during ventricular tachycardia (150/min) resulted in slowing of the ventricular rate (100/min) with the appearance of multifocal complexes. An additional 10 mg/kg of procaine amide produced a further reduction of the ventricular rate and a widening of the multifocal complexes. A third dose of 10 mg/kg of procaine amide slowed the ventricular rate to 60/min and ultimately ventricular arrest occurred. The control conduction data indicated that this animal had a preexistent ventricular conduction abnormality. The defective conduction was exacerbated by acetylstrophanthidin with and without pacing from the bundle of His (table 1, no. 14). This defect was not evident in the routine electrocardiogram. The implications of these findings will be discussed.

Effects of Diphenylhydantoin Sodium on the Normal Heart (Table 2)

Diphenylhydantoin sodium was administered in four animals to determine if its electrophysiological effects on the normal heart differed from its actions on the digitalis-intoxicated heart. In doses of 5 mg/kg, diphenylhydantoin sodium produced a marked depression of ventricular automaticity. No effect on intraventricular conduction was seen in three experiments, while there was minimal slowing of intraventricular conduction in the other lasting only 2 minutes. Diphenylhydantoin sodium caused enhancement of A-V conduction in three studies and had no effect in one (average change, 5.6%). No effect was seen on the sinus rate.

Effects of Procaine Amide on the Normal Heart

In two additional dogs, procaine amide was given in doses of 30 mg/kg following control measurements. It was found that procaine amide prolonged intraventricular and A-V conduction and slowed sinus rate. However, the intraventricular conduction was found to be increased by only 13 to 18% over control values in the normal heart as compared to an increase of 53 to 87% with comparable doses of procaine amide in the digitalis-intoxicated heart. The significance of this finding will be discussed. As previously mentioned, it was difficult to obtain data on the effect of procaine amide on ventricular automaticity.

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Discussion

In recent years, diphenylhydantoin sodium has been used in the treatment of digitalis-induced arrhythmias. Mosey and Tyler found it to be effective in abolishing the ventricular tachycardia resulting from digitalis toxicity in dogs and, more recently, its therapeutic value in aborting digitalis-induced arrhythmias has been confirmed. Studies of humans have also indicated that diphenylhydantoin sodium is particularly effective in treating arrhythmias caused by an excess of digitalis.

Little is known, however, about diphenylhydantoin sodium's mechanism of action as a
Table 2
Comparative Effects of Diphenylhydantoin Sodium and Procaine Amide on the Nondigitized Heart

| No. | Control | Time after administration of drug | | | | | 10 minutes |
|-----|---------|-----------------------------------|---|---|---|---|---|---|
|     | SR      | AVC     | IVC   | VET | SR      | AVC     | IVC   | VET |
| 1   | 160     | 67      | 63    | 21  | 150     | 66      | 64    | 43  | 140     | 67      | 63    | 28  | 150     | 67      | 62    | 26  |
| 2   | 140     | 100     | 85    | 34  | 140     | 92      | 85    | 45  | 140     | 100     | 85    | 41  | 140     | 100     | 85    | 36  |
| 3   | 180     | 71      | 62    | 28  | 180     | 68      | 62    | 41  | 180     | 68      | 63    | 36  | 180     | 63      | 63    | 38  |
| 4   | 160     | 78      | 69    | 16  | 160     | 72      | 69    | 34  | 160     | 72      | 69    | 34  | 160     | 72      | 69    | 30  |

Abbreviations: SR = sinus rate; AVC = atrioventricular conduction time (msec); RSR = regular sinus rhythm; IVC = intraventricular conduction time (msec); and VET = ventricular escape time (sec).

*Sinus escape beat.

Figure 5
Production of severe QRS aberration during pacing of bundle of H's with acetylstrophanthidin and procaine amide. (Top trace) Lead II of the electrocardiograms; (bottom trace) bundle of His pacing stimulus (HBPS). A continuous trace of pacing of bundle of H's (p.i. = pacing impulses) at 240/min. Note the progressive slowing of intraventricular conduction (85 to 97 msec) until an inverted, aberrant, and greatly prolonged QRS complex is produced.

cardiac anti-arrhythmic agent. The drug has been found to exert its anti-arrhythmic effect directly on the myocardium. It has been stated that diphenylhydantoin sodium transiently decreases conduction velocity, while others have reported that it has no significant effect on intraventricular conduction.

Our studies indicate that diphenylhydantoin sodium acts to decrease ventricular automaticity markedly in both the digitalis-intoxicated and the normal heart (fig. 1). In most cases it appears to have no discernible effect on intraventricular conduction (fig. 2), although in some instances a minimal, transient slowing was evident. In addition, from our data, it would appear that diphenylhydantoin sodium antagonizes the action of digitalis on the A-V node by decreasing the A-V block caused by the glycoside (fig. 3).

Procaine amide, a well-known anti-arrhythmic agent, has been shown to be effective in the treatment of ventricular arrhythmias,
but its value in treating those arrhythmias caused by digitalis has been questioned. Goldberg and Cotten\textsuperscript{14} produced ventricular tachycardia in 14 dogs with digitoxin or ouabain and produced reversion to normal sinus rhythm with intravenous procaine amide in eight of the animals. In the six other animals, however, procaine amide produced slow idioventricular rhythms followed in four animals by cardiac arrest. Zapata-Diaz and associates\textsuperscript{15} recognized that procaine amide may eliminate ventricular extrasystoles produced by digitalis, but their work also indicated that more severe and even fatal ventricular arrhythmias could result from its use. They suggested that the conduction disturbance that was produced by procaine amide facilitates “re-entry” type extrasystoles in the ventricle.

The present study confirms the fact that procaine amide does prolong intraventricular conduction (fig. 4), and more importantly, that this conduction delay is significantly accentuated in the digitalis-intoxicated heart as compared to the normal heart. Therefore, the chances of procaine amide potentiating a “re-entry” type of arrhythmia is greater with digitalis toxicity in which an intraventricular conduction impairment exists prior to administration of procaine amide. In one of our studies, procaine amide (10 mg/kg) caused a digitalis-induced unifocal ventricular tachycardia to become a slow multifocal ventricular arrhythmia which, in a short time, was followed by cardiac arrest. The records revealed that an underlying intraventricular conduction abnormality existed which was not evident in the routine electrocardiogram. In another experiment in which procaine amide was used, increasing the ventricular rate by pacing from the bundle of His produced progressive prolongation of the QRS at which time such severe aberration ensued that it could not be distinguished electrocardiographically from a ventricular flutter (fig. 5). By quickly lowering the rate of pacing below this critical level, the nonaberrant ventricular depolarization could always be restored. In contrast, diphenylhydantoin sodium produced insignificant changes in intraventricular conduction and in no case was QRS aberration seen at any rate (fig. 2).

In order to better understand the problems inherent in the use of anti-arrhythmic agents in treating digitalis toxicity, the physiological basis for digitalis’ arrhythmic action should be briefly examined. It has been shown that in addition to enhancing ventricular automaticity, digitalis also prolongs intraventricular conduction after 60 to 75% of the lethal dose is given.\textsuperscript{16, 17} Even lower doses of digitalis may impair conduction in the specialized cardiac fibers. This effect can be unmasked at lower doses by increasing the heart rate,\textsuperscript{18} as was clearly shown in the present study during pacing from the bundle of His.

It has been postulated that depression of ventricular conduction can lead to “re-entry” type extrasystoles. According to this theory, there is unidirectional block of the normal wave of excitation into an area of the Purkinje system. However, the impulse can enter this area in a retrograde direction at a time when the surrounding tissue is no longer refractory.\textsuperscript{19} In a study of ouabain-induced arrhythmias in the intact dog heart, Vassalle and associates\textsuperscript{20} found arrhythmias of a “re-entry” type in addition to those caused by enhanced automaticity.\textsuperscript{20} The “re-entry” arrhythmias were found to be rate dependent, increasing in frequency with fast rates and decreasing when the heart was slowed.

Alterations in intraventricular conduction as well as changes in automaticity induced by digitalis can thus produce ventricular arrhythmias. By slowing conduction, “re-entry” type arrhythmias can occur in a “blocked” area and by enhancing automaticity, self-sustaining arrhythmias can be established. The ideal therapeutic agent in the treatment of digitalis-induced ventricular arrhythmias, therefore, would be one that depresses automaticity while enhancing intraventricular conduction. Agents such as procaine amide can suppress digitalis-enhanced automaticity but
may potentiate a "re-entry" type arrhythmia by adding to the intraventricular conduction abnormality caused by the glycoside. In treating digitalis toxicity, our results indicate that diphenylhydantoin sodium is superior to therapeutic agents such as procaine amide since diphenylhydantoin sodium not only depresses automaticity but has little or no effect on intraventricular conduction.

In addition to its depressant effects on intraventricular conduction, procaine amide has been shown to have a direct depressant effect on A-V conduction. Our study demonstrates that procaine amide and digitalis can be additive in blocking A-V conduction. As has been stated, diphenylhydantoin sodium, in contrast to procaine amide, appears to antagonize the digitalis effect on the A-V node, thus improving A-V conduction in the digitalis-intoxicated heart.

It is felt, therefore, that since diphenylhydantoin sodium depresses automaticity and enhances A-V conduction while having little or no effect on intraventricular conduction, it is an excellent therapeutic agent in treating excesses of digitalis. These physiological properties of diphenylhydantoin sodium account for its effectiveness, as well as its therapeutic safety in the treatment of digitalis-induced arrhythmias.

Acknowledgment

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References

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SCIENCE AS THE SPHINX

Sphinx, says the story, was a monster combining many shapes in one. She had the face and voice of a virgin, the wings of a bird, the claws of a griffin. She dwelt on the ridge of a mountain near Thebes and infested the roads, lying in ambush for travellers, whom she would suddenly attack and lay hold of; and when she had mastered them, she pounded to them certain dark and perplexed riddles, which she was thought to have obtained from the Muses. And if the wretched captives could not at once solve and interpret the same, as they stood hesitating and confused she cruelly tore them to pieces.

The fable is an elegant and wise one, invented apparently in allusion to Science; especially in its application to practical life. Science, being the wonder of the ignorant and unskilful, may be not absurdly called a monster. In figure and aspect it is represented as many-shaped, in allusion to the immense variety of matter with which it deals. It is said to have the face and voice of a woman, in respect of its beauty and facility of utterance. Wings are added because the sciences and the discoveries of science spread and fly abroad in an instant; the communication of knowledge being like that of one candle with another, which lights up at once. Claws, sharp and hooked, are ascribed to it with great elegance, because the axioms and arguments of science penetrate and hold fast the mind, so that it has no means of evasion or escape; a point which the sacred philosopher also noted: *The words of the wise are as goads, and as nails driven deep in.* Again, all knowledge may be regarded as having its station on the heights of mountains; for it is deservedly esteemed a thing sublime and lofty, which looks down upon ignorance as from an eminence, and has moreover a spacious prospect on every side, such as we find on hill-tops. It is described as infesting the roads, because at every turn in the journey or pilgrimage of human life, matter and occasion for study assails and encounters us. Again Sphinx proposes to men a variety of hard questions and riddles which she received from the Muses. In these, while they remain with the Muses, there is probably no cruelty: for so long as the object of meditation and inquiry is merely to know, the understanding is not oppressed or straitened by it, but is free to wander and expatiate, and finds in the very uncertainty of conclusion and variety of choice a certain pleasure and delight; but when they pass from Muses to Sphinx, that is from contemplation to practice, whereby there is necessity for present action, choice, and decision, then they begin to be painful and cruel; and unless they be solved and disposed of, they strangely torment and worry the mind, pulling it first this way and then that, and fairly tearing it to pieces. Moreover the riddles of the Sphinx have always a twofold condition attached to them; distraction and laceration of mind, if you fail to solve them; if you succeed, a kingdom.—Selected Writings of Francis Bacon. New York, The Modern Library (Random House), 1955, p. 417.
The Electrophysiological Properties of Diphenylhydantoin Sodium as Compared to Procaine Amide in the Normal and Digitalis-Intoxicated Heart

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