CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

XV. Hereditary Stenosis of the His Bundle in Pug Dogs

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SUMMARY

Syncope and sudden death occurs in certain purebred Pug dogs which have been found to have intermittent sinus pauses and paroxysmal second degree heart block on electrocardiographic (ECG) study. We have established a colony of such dogs to study this problem and here report the results of histological examination of the cardiac conduction system in twenty-one of them. These include a dam which may be considered the proband, three of her offspring (two littermates) and three fetal pups in an unborn litter of one of these; three of the four adult dogs died suddenly and unexpectedly. Two groups of puppies descendants of these lines were also studied after they all died within three days of birth. The first group of puppies (8) did not have suitable ECG studies but the second group (6) did and showed ECG changes similar to those in the adult dogs. In all 21 dogs the sinus node was anatomically normal, but in every one there was significant stenosis of the midportion of the His bundle. There was no abnormality of the atrioventricular (A-V) node or of the bundle branches, and the cardiac valves and coronary arteries were normal. Two pups had ventricular septal defects and one of these had an atrial defect as well. All the dogs were of the normal fawn color, had a normal physical appearance and no visible evidence of associated extracardiac abnormalities. The adult dogs were able to hear normally but the puppies died too early to test their hearing. The paroxysmal heart block may in part be attributable to the abnormality in the His bundle, but other factors possibly leading to heart block and long sinus pauses are discussed. Stenosis of the midportion of the His bundle appears to be a heritable trait in these purebred Pug dogs.

AESOP'S FABLES are literary classics full of lessons which man can learn from other animals. In addition to the philosophical lessons taught from these fables, there are many biological principles which can be elucidated by careful observations in different species of animals. Examples include a number of recent investigations in comparative cardiology, some of which have dealt with the subject of sudden death in dogs.1-3

A few years ago three Pug dogs from a line which had syncope attacks and a tendency to die suddenly and unexpectedly were brought to the Auburn University Small Animal Clinic. Electrocardiograms made on some of the Pug dogs with syncope demonstrated various forms of electrical instability of the heart. A colony of Pug dogs has now been established for the purpose of careful investigation into the anatomical and physiological basis for the electrical instability and into the pathogenesis of the syncope and sudden death. This report will present the result of some of those investigations.

Material and Methods

Several years ago a five-year-old purebred female Pug dog (to be designated Dog A) was examined because of a history of syncopal attacks. An electrocardiogram made with Dog A lying quietly awake (no sedation) is shown in figure 1 and is typical of a number of such records. The syncopal attacks had a characteristic course which began with a few seconds of excitement and hyperactivity ending in an abrupt collapse. Dog A was observed during several attacks, which consisted of dyspnea, cyanosis, disorientation and the absence of any audible heartbeat. Within the next few minutes the dog would gradually recover. This sequence, including the onset with a period of excitement, is remarkably similar to the observed spells of syncope in congenitally deaf children.2-4 In the second year of observation Dog A died suddenly and unexpectedly after being observed a few minutes earlier in apparent good health.

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An autopsy was performed and no gross or microscopic abnormalities were found except in the heart. Special examinations of the heart included the sinus node and atrioventricular (A-V) junctional region encompassing the A-V node and His bundle. Although the sinus node of Dog A was normal, the His bundle was markedly narrowed and abnormally fibrotic near its midpoint. In this dog and in all others of the present report, there was specifically no other abnormality of the cardiac valves or the coronary arteries, nor of the myocardium (except septal defects as noted later). None of these dogs was deaf, a trait associated with cardiac electrical instability in man and in the Dalmatian coach hound, and nor was there any abnormal pigmentation or physical deformity.

Dog A was mated to another Pug dog reported to have such syncopal attacks, producing a litter of four pups. Two of these pups were obtained and will be designated Dogs B and C. The sire of these two pups was lost to follow-up because that owner did not wish further study of the dog. Dog B was female and Dog C male. Both began having syncopal attacks within the first few months of life, and these spells were identical in form to those of Dog A. It is possible that transient earlier spells were missed. A typical electrocardiogram of Dog B is shown in figure 1 and is similar to ones from Dog C.

Dog B died suddenly and unexpectedly in the third year of life. Dog C lived for five years and was found dead unexpectedly, at last previous observation having been in his usual good health except for recurring spells of unconsciousness. Similar special histological studies of the cardiac conduction system were made in Dogs B and C as in Dog A. The sinus nodes were again normal (fig. 2). The only abnormality was in the His bundle, which exhibited narrowing in its midportion (fig. 3), exactly the same in both dogs as in their dam.

During the period of observation of Dog B, she was mated with another purebred Pug which was having syncopal attacks. Dog B died about two weeks prior to the predicted time of whelping and all three fetuses died with her. Because of the suspected hereditary transmissability of defective development of the His bundle, all three fetal hearts were serially sectioned at 6 micron intervals to study the cardiac conduction system. The sinus node and other components of the hearts were normal, except for the His bundle. In each of these three fetal pups the His bundle was stenotic near its midpoint (fig. 4).

A fourth adult Pug dog (Dog D) exhibited paroxysmal second degree A-V block on numerous electrocardiograms. Dog D was descended from Dog A through both maternal and...
paternal pathways. This dog was sacrificed at the age of two years to examine a technique of electrode placement. The only abnormality at necropsy examination was the same marked narrowing of the His bundle found in the other dead Pug dogs.

It was now apparent that we were dealing with a hereditary developmental fault of the His bundle which was associated with syncopal attacks and sudden death. While the mode of genetic transmission is a subject of continuing study, it appears to be an autosomal recessive trait with a high degree of penetrance. To the present time we have been unable to identify any associated fault such as deafness, joint or other bony abnormalities, pigmented anomaly of the eyes or coat, nor any consistent additional cardiac abnormality. Because of interest and cooperation by several owners and breeders of Pug dogs, we have now established a colony for the sake of further study of the exact incidence and nature of the underlying cardiac problem. All these are purebred Pug dogs and have been of the fawn color with normal markings of the face and ears and normal general appearance and build.

By the fourth generation of dogs in the colony, most pups in each litter died within 24 to 72 hours of birth. Eight such pup hearts were chosen for serial section study of the conduction system. All eight had the same sire (also the sire of Dog D), but each of the four pairs had a different dam. The litter pairs are identified as E, F, G and H and littermates are identified by serial numbers attached to these letters, e.g., E-1 and E-2. Both pups in litters E, G and H exhibited the typical marked narrowing of the midportion of the His bundle (figs. 5–7), while pups F-1 and F-2 showed only a minor and moderate degree of such narrowing, respectively. Satisfactory electrocardiograms were not obtained on these eight pups.

At a later date we established a system for telemetered electrocardiograms to be recorded periodically from all newborn pups in the colony. Electrodes for the purpose were attached over the xiphoid and the manubrium in a standard

Figure 3

Sections from the A-V node, midportion of His bundle and anterior portion of His bundle of Dog B are illustrated in A, B and C, respectively. Arrows outline the A-V node and the two portions of His bundle. The magnification reference bar in B applies to all three photomicrographs. In its midportion the His bundle was both narrowed and fibrotic. ECG from this dog is in lower part of figure 1.
position for bipolar recordings, and a radio transmitter permitted magnetic taping of these tracings. In addition to occasional examples of A-V block, a more prominent electrocardiographic abnormality was the occurrence of prolonged sinus pauses (fig. 8). A similar abnormality was subsequently observed in an adult Pug dog (I) which was a littermate of Dog D and was having syncopal spells (fig. 9). In Dog I and in three of the six pups with telemetered ECGs, atropine sulfate (0.05 mg/lb) was administered and completely eliminated the previously very frequent prolonged sinus pauses. Atropine also appeared to eliminate the bouts of A-V block, although these were much less frequent than the sinus pauses and the effect of atropine on the block was therefore less certain.

Dog I is still alive at this time. Of the monitored pups, three litter pairs died in the first three days of life; the litter pairs are identified as J, K and L. Five of these six pups had prolonged sinus pauses, with lesser examples of some degree of A-V block; the sixth pup (L-2) had a sustained supraventricular tachycardia at 170 per minute. Pups K-1 and K-2 were both being monitored (by chance) at the time of death and the ECG showed progressive slowing of the sinus rhythm until cardiac standstill, without concomitant A-V block of any degree. However, in Pup K-1 there was a minor degree of QRS broadening intermittently; this was the only example of abnormal QRS configuration in the entire study, all other dogs having normal QRS configuration in every recorded ECG. The exact terminal ECG is not known in the other four monitored pups. In Pup J-2 atropine was administered and completely abolished the frequent prolonged sinus pauses and caused the expected sinus tachycardia; about 30 minutes later the heart abruptly stopped and that dog died. In all six monitored pups the sinus node was readily identified and appeared normal for the newborn heart. All six pups had significant narrowing of the midportion of their His bundles, the degree of stenosis being marked in J-1 (fig. 10), K-1 (fig. 11) and L-2, moderate in J-2 and K-2 and minor in L-1.

![Figure 4](image1)

**Figure 4**

These three photomicrographs are from the heart of the first fetal puppy of Dog B. Arrows outline both the A-V node (AVN) and His bundle (AVB). The His bundle is narrowed in B, a section made about 1.4 mm anterior to A and 0.54 mm posterior to C. Magnification (reference bar in C) is the same in all three photomicrographs.

![Figure 5](image2)

**Figure 5**

Five photomicrographs of the A-V node and His bundle from puppy E-2 illustrate marked stenosis of the midportion of the His bundle, arrow in C. TV and MV are the tricuspid and mitral valves, orientation being the same in each section. All five sections are sequential, chosen from serial sections. Except for the distance between sections B and C, which is about 0.7 mm, the distance between each other section is about 0.28 mm. Magnification (reference bar in B) is the same in all five photomicrographs. More details of C, D and E are seen in figure 6.
Because Grant once suggested that the interventricular foramen may normally remain patent postnatally, only to close during the newborn period in an indeterminate but possibly large percentage of human hearts, we examined each heart for this question. There were no ventricular or atrial septal defects in 19 dogs, but two dogs (H-1 and K-1) did have patent interventricular foramen (fig. 12). That was the only septal fault in H-1, but K-1 additionally had a second ventricular septal defect in the muscular portion of the septum, plus a secundum type atrial septal defect. Pup K-1 was also the only dog in the group to have intermittent broadening of QRS complexes.

Discussion

Successful animal husbandry is the result of careful observation and analysis combined with certain intuitive judgments. In these respects it is neither more nor less precise than most biological sciences. Because some breeds of animals have been fancied by owners for centuries or even millennia, it is remarkable that these popular breeds have been preserved in many respects unchanged in appearance without the introduction of non-visible lethal traits. Much of this success must be attributable to the intuitive or pragmatic identification of some associated non-lethal but visible trait which the knowledgeable breeder can

![Figure 6](http://circ.ahajournals.org/)

Higher magnification photomicrographs of the His bundle (arrows) of puppy E-2 illustrate its progressive increase in diameter proceeding from the midportion (A) anteriorly. Magnification reference bar in B applies to all three sections.

then avoid. For example, breeders of Dalmatian coach dogs know that pups which develop abnormally large pigmented spots (known among cognoscenti as "patched dogs") are apt to be deaf and have a predisposition to sudden death.

It is apparent from our present study that a lethal cardiac trait can be heritably transmitted without the association of a visibly recognizable external trait, at least so far as we are presently able to discern. One is not so surprised that such a trait would eventually appear in the Pug dog, but that it has not appeared before now in a breed fancied in the Western world for at least four centuries and in China an indeterminate time before that. We can assume that with the Pug dog and probably most successfully bred animal strains, owners and breeders soon learn of a high incidence of either unexplained deaths or visible deformities and simply avoid use of animals from suspect lines for future breeding. Furthermore, certain breeding principles such as periodic outcrossing reduce the likelihood of unintentional intensification of undesirable traits, some perhaps unrecognized.

Two previous investigations of sudden death in purebred dogs have also provided evidence of a
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Figure 7
Narrowing of the His bundle of puppy G-1 is shown in B, for comparison to the A-V node in A and anterior portion of His bundle in C. Magnification for all three sections is shown in C.

heritable cardiac fault causing electrical instability of the heart. In patched Dalmatian coach hounds that are usually born deaf, it is the sinus node and multiple atrial arteries which are abnormal, and sinus rhythm is unstable. In Doberman pinschers there is a transecting fatty degeneration of the His bundle which is principally manifest during the prime of life of those dogs (ages 3 to 7 years). Of thirteen Doberman dogs dying suddenly, every one had the same fatty degenerative lesion in the His bundle accompanied by metaplasia of collagen in the central fibrous body into cartilage and the formation of actual bone cysts directly adjacent to the His bundle. In that study it was concluded that both the metaplasia in the central fibrous body and the degeneration of the His bundle were most likely the consequence of local ischemia caused by narrowing of nutrient arteries of the region. A third clinicopathologic correlation, possibly bearing on the present report, described complete heart block in a mongrel dog with apparent failure of maturation

of individual cells in both the sinus node and A-V node. However, in that dog the sinus node, A-V node and His bundle were normally shaped and located.

In our Pug dogs the histologic appearance and location of narrowing in the His bundle suggests that there was embryological failure of proper union between the A-V node migrating inward and His bundle developing in situ. But while there seems little question that stenosis of the midportion of the His bundle was a consistent heritable fault in these purebred Pug dogs, being present in every one of the 21 hearts studied histologically, its functional significance and the mechanisms of death are not so straightforward. In the adult dogs each was shown to have paroxysmal heart block which can be logically related to the histological abnormality. But at least one of the adult dogs (Dog I) and most of the puppies had prolonged periods of sinus pauses and less striking and inconsistent degrees of heart block. Furthermore, the sinus pauses (and possibly the heart block) were abolished with atropine.

The episodes of recorded heart block were both phasically incremental (Mobitz type I, or Wenckebach cycles) and of an abrupt nature (Mobitz type II). Both types of block could be documented in the same dog at different times. We do not presently

Figure 8
This ECG from puppy J-1 shows two long sinus pauses marked with black dots, the second longer than the first. All four segments of tracing are continuous. See also figure 10.

Figure 9
This ECG (continuous strips) is from Dog I, still alive. Nonconducted sinus beats (arrows) are preceded by little if any P-R interval prolongation in those instances, whereas distinct incremental first degree heart block is seen at other times (asterisk).
have sufficient observations to say whether atropine differentially influenced these two types of block, but recognize that this would be useful to know. Since some have suggested that the fault in Mobitz type I block is usually in the A-V node, and in Mobitz type II in the His bundle or proximal bundle branches, it is significant that the A-V node and both bundle branches were anatomically normal in all 21 hearts examined. Although this need not mean that the A-V node and bundle branches are physiologically normal, the consistent presence of abnormal stenosis in the midportion of the His bundle leads us to focus our attention on it.

There are four findings in our study which help define both the pathogenesis and functional significance of the stenosis of the His bundle. First, it was present in all three fetal hearts in the unborn litter of Dog B, thus clearly separating this abnormality of the His bundle from the normal postnatal molding and shaping of the A-V node and His bundle which never begins in utero. Second, two of the 21 dogs had a patent interventricular foramen and it is tempting to relate this fault to a genetically determined maldevelopment of the closely adjacent His bundle. A patent interventricular foramen does not appear to be associated with the normal postnatal molding and shaping of the A-V node and His bundle within the central fibrous body. Third, none of the dogs at any age had sustained heart block, demonstrating that the stenotic His bundle usually conducted satisfactorily but failed intermittently. Fourth, although there was a very high perinatal mortality in later generations of the colony, some of the dogs lived for several years, suggesting that the stenotic process was not progressive or at least not very rapidly. The fact that syncopal attacks kept recurring, that the dogs died suddenly and unexpectedly even at the age of several years, and that there was excessive fibrosis in the stenotic portion of the His bundle in the adult dogs all indicate that the His bundle was congenitally faulty and never recovered stable normal function.

It is important to consider that the A-V junctional region has two normal functions in the heart: (1) conduction from atrium to ventricle, and (2) serving as the primary source of subsidiary pacemaking activity. Both congenital and acquired abnormalities in the A-V junctional region which cause complete heart block are known to be compatible with survival because a subsidiary A-V junctional pacemaker assumes command of ventricular function. Just where the A-V junctional pacemaking site is located from a histological or cytological standpoint is presently uncertain. Recent studies from this laboratory have demonstrated two levels of rate for escape A-V junctional rhythm, one very slow and the other not, but both of which probably originate from the same or very closely apposed sites in the A-V junctional region of the dog.10-12

One possible unifying explanation for the electrophysiological and the anatomical abnormalities observed in these Pug dogs would be that the normal site of automaticity for stable cardiac performance has to be above the observed narrowing in the midportion of the His bundle. Then if conduction through that narrowed portion failed for any reason, whether it was because of critically severe structural narrowing or a lesser narrowing coupled with the negative dromotropic and negative chronotropic effect of excessive vagal tone, then the only effective A-V junctional pacemaker would lose its value because it was located above the level of A-V block. Although many...
would counter that some more distal automatic site should emerge, we have failed to find any more distal automaticity of a stable nature in a large number of intact canine hearts studied in situ.\textsuperscript{10, 11}

Sinus pauses in puppies (and presumably other animals, possibly including human babies) might be less striking if an A-V junctional subsidiary pacemaker regularly and phasically emerged. In the preceding reasoning it was deduced that such an escape pacemaker might be precluded from being effective by being located above the site of morphological maldevelopment (narrowing) of the His bundle. Both puppies and babies normally have a widely variable level of resting vagal tone, as do awake adult dogs,\textsuperscript{13, 14} and this might further compound both the conduction failure with A-V block and the markedly prolonged sinus pauses with rare and ineffective A-V junctional escape. Elimination of the vagal influence with atropine did not prevent death in some of the pups, in which there was progressive slowing of sinus rhythm until cardiac standstill, suggesting that some additional factor possibly influences the stability of sinus rhythm. We have recently found that both sinus rhythm and A-V junctional rhythm in dogs depend on normal adrenergic neural tone (not circulating catecholamines) for their stable performance, but that A-V junctional rhythm in particular is so dependent.\textsuperscript{15}

Whether poor adrenergic neural tone contributes to the problem in our Pug dogs merits further investigation.

Since the sinus nodes in all the hearts from this line of Pug dogs appeared histologically normal, there is at least anatomical reason to expect that they were capable of normal impulse formation. However, for the long continued stability normally required of the sinus node, some feedback control would be a useful support mechanism. Various possible servomechanisms adding stability to the performance of the sinus node have been the subject of a recent review.\textsuperscript{16} From the present study it is reasonable to speculate that abnormal function by the A-V junctional region may not only be expressed by periodic failure of A-V conduction and ineffective escape of A-V junctional rhythm, but also by removing an important component of a stabilizing servomechanism for the sinus node. Various investigators have considered that the automaticity of the region of the sinus node and the region of the A-V junction behaves in a fashion resembling coupled relaxation oscillators, each adding stability to the performance of the other.\textsuperscript{16-19} If we consider the hearts of these Pug dogs in that fashion, then it may be the hereditary stenosis of the His bundle which is responsible not only for the episodes of heart block and failure of an effective A-V junctional escape rhythm, but perhaps also for the unstable performance of the sinus node.

\textbf{Figure 11}

Stenosis of the midportion of the His bundle of puppy K-1 is shown in B between sections of A-V node (A) and distal His bundle (C). Magnification for all three photomicrographs is given in B. See also figure 12.
Figure 12

Puppy K-1 had two ventricular septal defects and a secundum type atrial septal defect. One defect (VSD-1) shown in A was through the muscular septum below the location of the A-V node (AVN), while the other defect (VSD-2) shown in B, was through the region of the membranous septum and thus represents a persistent interventricular foramen directly above the anterior portion of His bundle (AVB). Magnification for both sections is given in A.

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