Advanced Disturbances of the Cardiac Mechanism in Potassium Intoxication in Man

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The use of the artificial kidney at the Peter Bent Brigham Hospital in the treatment of acute renal shutdown has afforded a unique and extensive opportunity to study the disturbances of rhythm and conduction occurring in potassium intoxication. In this theoretic, and at times frankly speculative, paper the authors present evidence which suggests the applicability to man of Wiggers’ views based upon animal experimentation, namely that the ectopic rhythms developing in this condition arise “by default” (escape mechanisms) rather than “by usurpation” (increased excitability) and that potassium exerts its early and preponderant effect upon the subendocardial layers of the human ventricle.

The various arrhythmias developing during the course of potassium poisoning have interested many observers. Sinus slowing, 1-4 sinus arrhythmia, auricular standstill, auriculoventricular block, 2, 3, 5, 6 auricular fibrillation, 6-9 ectopic ventricular beats, 7 ventricular tachycardia, 1, 6, 7 ventricular fibrillation 2, 3, 6, 7 and ventricular standstill 2, 3, 4, 6, 10, 11 have been reported. First degree heart block has been a common finding. Although in the pre-electrocardiographic era higher grades of auriculoventricular block had been mentioned 9 and are reported to have occurred once in a canine experiment, 10 they have not been noted in man. Since the P waves are apt to become lost because of their prolongation and the decrease in their amplitude, and because they may be engulfed in the preceding ventricular complex, their recognition, and accordingly the recognition of the higher grades of auriculoventricular block, is difficult if not impossible. By the same token it is exceedingly difficult under the circumstances to distinguish between sinus arrhythmia and auricular fibrillation. While there is no question about the common occurrence of sinus slowing and arrhythmia when the P waves are still easily recognized, a grossly irregular rhythm recorded when the P waves are absent or are no longer recognized with certainty as such, could be due as well to sinus arrhythmia with persistent sinus activity as to auricular fibrillation. A third but less likely explanation for the irregular ventricular rhythm might be auricular standstill with arrhythmia of the ventricular pacemaker.

The disturbances in the ventricular mechanism developing during potassium intoxication have been even more puzzling to physiologists. Two curious sets of observations have demanded explanation. These are: (1) the inceptive of ectopic rhythms while the organism is under the influence of a substance whose physiologic effect has long been regarded as an inhibitor of the myocardium and (2) the development of ventricular tachycardia or fibrillation under certain circumstances associated with potassium excess and their inhibition under other conditions associated with potassium excess.

Hering 7 and later Nahum and Hoffer 1 sought to explain these apparent discrepancies by assuming the simultaneous operation of two differing effects of potassium on cardiac receptors. Thus Hering 7 postulated a primary...
inhibitory action upon the so-called normotropic centers (sinus slowing, auriculoventricular block and intraventricular block) and a stimulating influence upon the so-called heterotopic centers (extrasystoles, paroxysmal ventricular tachycardia, ventricular fibrillation). Without assuming different types of receptors Nahum and Hoff\(^\text{1}\) pointed out that whereas potassium, if infused slowly, produces widespread inhibition of cardiac automaticity culminating in complete standstill, it may, if infused rapidly, enhance cardiac automaticity. They regarded the development of foci of increased automaticity in the presence of intraventricular block as resulting in the incoordination which is ventricular fibrillation. MacWilliam,\(^\text{12}\) on the other hand, attributed a purely depressive effect to potassium, emphasizing that, in conditions of depressed conduction, stimuli not faster than rates commonly seen when the heart is beating in coordinated fashion, may cause fibrillation. Wiggers, Theisen and Shaw\(^\text{13}\) maintained that potassium depresses conduction, first in the bundle branches and internal layers of the ventricle, and subsequently in diverse portions of the myocardium; incoordination follows when some fractions escape complete inhibition, but total cessation occurs when all portions of the myocardium are completely depressed.

It has been suggested that a study of the earlier stages preceding the onset of potassium fibrillation might cast some light upon its mechanism. Hering considered ventricular premature beats an essential preliminary. Nahum and Hoff found no extrasystoles but observed widening of the QRS complex and changes in the S-T segment and in the T wave as forerunners of fibrillation. Wiggers and associates noted sinus slowing and depression of auriculoventricular conduction as constant findings; instances of premature ventricular beats (perhaps actually ventricular escape) were present in some but by no means all of their experiments. They concluded that premature beats are an incidental phenomenon and not an essential prelude to fibrillation.

It is quite generally agreed that intraventricular block is an important feature of all but the very earliest stages of potassium intoxication. The question has arisen whether: (1) this disturbance in transmission of the impulse is limited to the specialized conducting tissue of the heart; (2) all myocardial tissue, ventricular muscle proper, bundle branches and subendocardial Purkinje network alike, are involved indiscriminately; (3) conduction is first impaired in the bundle branches and subendocardial fibers, then in other parts of the ventricular myocardium,\(^\text{13}\) or (4) there is a diffuse interference with spread of the wave of excitation, with the cells of the conduction system being more susceptible to potassium excess than the rest of the heart.\(^\text{14}\)

In the normal heart the beginning of the QRS complex corresponds to the beginning of activation of the ventricular muscle proper, more particularly that of the septum. Conduction in the bundle branches and in the subendocardial Purkinje tissue is actually included in the P-R interval. But conduction is normally so extremely rapid in these tissues that it does not last long enough to be registered as a visible part of the P-R interval. Accordingly, the time consumed in the bundle branches is not represented in the normal electrocardiogram. The prolongation of the QRS complex in the bundle branch block is actually due to unidirectional activation of the interventricular septum and eccentric excitation of ventricular muscle proper. The diagnosis of bundle branch block is made rather upon the inferential evidence of an abnormal delay in the electrical activation of one ventricle or the other.\(^\text{15}\) The literature contains very little evidence for bundle branch block in potassium poisoning. Experimental studies, in the manner of Lewis, of the heart poisoned with potassium have not yet been reported. Hence, although we know that the P-R interval is prolonged in hyperkalemia, it is not known just how much of the P-R interval represents transmission of the impulse in the bundle branches. In one canine experiment Nahum and Hoff\(^\text{14}\) found that at an advanced stage of potassium intoxication the left ventricle contracted 0.05 second before the right ventricle. Concealing the existence of diffuse intraventricular block these authors concluded that right bundle branch block was also present. Finch and co-workers,\(^\text{16}\) recognizing the gross resemblance between the tracings of
bundle branch block and the biphasic potassium curves, applied the criteria of Wilson to the study of the bipolar chest leads in potassium poisoning. They were unable to confirm the existence of bundle branch block and concluded that the changes could more logically be ascribed to general impairment of conduction throughout the heart. In the experimental animal pure bundle branch block is rarely associated with a duration of the initial ventricular complex exceeding 0.12 second by more than a few hundredths of a second. If this figure is greatly exceeded, as it is apt to be in the more advanced stages of potassium intoxication, the conduction defect cannot be explained by the bundle branch block alone; it is then necessary to assume a greater or lesser degree of impaired conduction in the ventricular muscle proper.

With these considerations in mind it is our purpose in this paper to present observations on six cases of potassium intoxication in which advanced disturbances of the cardiac mechanism were recorded. These cases were culled from a total experience at this writing with 30 hyperkalemic patients. Other aspects of 3 of them (cases 1, 3 and 4) have been described in another communication.17

Case 1. Ventricular escape, flutter, tachycardia and fibrillation: auricular fibrillation in potassium intoxication. J. M. C., PBH S941, a South American newspaperman with chronic rheumatic valvular heart disease was admitted in uremia on Oct. 19, 1948. The only abnormality in the admission electrocardiograms was low electromotive force. The first three weeks of his hospitalization were characterized by evidences of severe acute infection and nitrogen retention. On November 13 there was an abrupt and striking change in his appearance. He developed a flaccid paralysis which began in his legs and spread to his arms and apparently involved the muscles of respiration. Electrocardiograms (fig. 1) recorded at this time were quite typical of potassium intoxication. The ventricular rhythm was slightly irregular, the rate 74 beats to the minute. The QRS complexes were bizarre and broad, measuring 0.16 second in duration. There were deep, wide negative deflections (usually S waves) in the conventional leads and in the unipolar chest leads. The T waves were tall and pointed, especially in leads V3–5. In leads V2–4 the segment leading from the nadir of the S wave to the peak of the T wave was an almost straight line. P waves were recorded in lead III but were much more clearly visible in lead V1. A continuous recording of lead II with the direct-writing electrocardiograph was commenced at 12:10, when further disintegration of the ventricular complexes was observed (fig. 2A). The QRS interval now measured approximately 0.28 second and the trace was in almost continuous motion, the rhythm was quite regular, and the heart rate 115 beats to the minute. At this point, the serum potassium level was 9.8 mEq./L. At 12:45 (fig. 2B) the rate of the heart slowed appreciably, the rhythm became grossly irregular again and the ventricular complexes somewhat sharper, the QRS complex measuring 0.16 second (fig. 2C). At 12:53 the trace abruptly developed a continuous sinusoidal appearance (fig. 2D) resembling that described in the electrocardiographic literature as characteristic of ventricular flutter. The rate was 155 beats to the minute. At this point an intravenous infusion containing 75 Gm. of glucose with 35 units of crystalline zinc insulin in 500 cc. of water was commenced.* During the first few minutes of this infusion, this continuous motion of the baseline persisted but the complexes became somewhat

* The rationale of the various forms of therapy employed in this study is described in detail in the companion publication.17
sharper, now resembling more closely the complexes of ventricular tachycardia. The rate of the heart increased to 184 beats to the minute (fig. 2E, F). A 3 per cent solution of sodium chloride containing 5 units of insulin was infused. The ventricular complexes became sharper and the rate slowed to 90 beats to

Fig. 2. Case 1. Fragments of continuous recording of lead II. A. Regular rapid rhythm (rate 115) showing further disintegration of the ventricular complexes. B. Thirty-five minutes later showing return to appearance noted in figure 1. C. Same five minutes later. D. Ventricular "flutter" at rate of 155; glucose-insulin infusion begun at this point. E. Ventricular "tachycardia" at the rate of 180 during glucose-insulin infusion. F. Same at rate of 184; glucose-insulin infusion continued. G. Return to appearance noted in C; glucose-insulin continued. H. Following sodium chloride and insulin showing shortening of QRS complex and return of P waves with sinus arrhythmia. I. Same at completion of saline-insulin infusion. J. Ectopic ventricular (escape) beat shortly after the beginning of normal saline infusion. K. A series of such beats beginning as escape mechanism; rate before sequence 140, during sequence 107.

Toward the end of the infusion the complexes again resumed (fig. 2G) approximately the form they had at 12:50. Shortly after this, the glucose-insulin infusion having been completed, 500 cc. of 3 per minute (fig. 2H) but intraventricular block persisted. In this strip a small oscillation was recorded, probably representing auricular activity (a small P wave is noted in the long pause preceding the third
complex from the end of the strip). At 1:15 when the saline-insulin infusion had been completed, there was very little further change in the appearance of the tracing (fig. 2J). At about this time infusion of 150 cc. of physiologic solution of sodium chloride was begun. Shortly afterward an ectopic beat was recorded (indicated by arrow in fig. 2J) with a configuration opposite the other complexes in that lead. This beat was not premature but developed rather after a long pause, suggesting an escape mechanism. In strip 2K a succession of such beats was recorded, again beginning as an escape mechanism rather than prematurely. Furthermore the ventricular rate during this salvo of ectopic beats was slower than the ventricular rate previous and subsequent to the "paroxysm." It is of some interest that the same type of broad ventricular complex was inscribed whether the ventricle was activated in the usual or in an opposite direction.* This suggests a diffuse slowing in ventricular activation regardless of the point of origin of the impulse. Here, then, was a sequence of six ectopic ventricular beats beginning as an escape or release phenomenon.

Figure 3A represents the complete set of tracings (of which figure 2K is lead II) taken at 1:25 following the completion of the infusion. At this time the patient had received a total of 22.6 Gm. of sodium chloride, 87.5 Gm. of glucose and 40 units of crystalline zinc insulin. The serum potassium had fallen from 9.8 mEq. per L. before the infusion to 8.0 mEq. per L. after the infusion. The QRS complex measured 0.14 second, the S waves were deep, T waves in precordial leads were still tall and pointed but P waves were not visible. In short, although there had been some improvement in the appearance of the complexes, they still showed characteristic changes of potassium intoxication.

The patient's blood was then dialyzed by the artificial kidney (hemodialysis) over the course of three hours. With the transfusion administered in the course of this dialyzing procedure, the patient received another 6 Gm. (approximately) of sodium chloride. When the dialysis was concluded, the serum potassium level had fallen from 8.0 to 5.7 mEq. per L., and the electrocardiogram showed striking improvement, the only remaining changes of hyperkalemia being minimal pointing of the T waves in leads V2-4, low voltage in the limb leads and irregularity of the ventricular rhythm.

The patient received digitalis for the first time after the last postdialysis tracing was recorded. Hence, none of the changes produced up to this point can be attributed to digitalis. During the six hours following the commencement of digitalization the ventricular rate slowed to normal; within the next 12 hours the tracings exhibited normal sinus rhythm, the P-R interval was at the upper limits of normal (0.20 second), the ventricular rate was 85 beats to the minute but low voltage persisted in the limb leads. One day later the tracings were unchanged. It is apparent that the changes induced by the artificial kidney persisted for 48 hours despite the lack of any treatment other than digitalis.

During the subsequent week the patient's clinical state was precarious and observations on the relative efficacy of various chemical forms of treatment and of hemodialysis were carried out. These are described in case 1 of the collateral study17 and are not relevant to the present discussion. A second dialysis (one week after the first) was followed by a slight transitory improvement, but after a day or two his condition deteriorated progressively and for the first time a pericardial friction rub was heard. Tracings taken on the third day showed first degree block (P-R interval 0.24 second), intraventricular block (QRS 0.11 second) and low electromotive force. The following evening he developed nausea and vomiting and at 9 p.m. complained of numbness in the arms. At 10:15 he became quite excited. At 10:30 the biceps reflexes could not be elicited. Tracings taken shortly thereafter (figure 4) resembled those obtained at the onset of potassium intoxication.

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* Wilson and Herrmann18 commented upon this same striking broadening of the ventricular premature beats occurring in a patient with terminal uremia and oliguria, attributing this peculiar form to a "toxic" depression of the conductivity of the Purkinje system.

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Fig. 3. Case 1. A. Complete set of tracings following infusions showing persistent changes of potassium intoxication. Note sharp pointing of the T waves. B. Same following artificial kidney showing disappearance of all changes except low voltage and emergence of grossly irregular rhythm, probably auricular fibrillation. The T waves are still pointed.
intoxication (fig. 1) showing intraventricular block (QRS 0.28 second), auricular standstill and a gross irregularity of the ventricles. The ventricular complexes in the standard limb leads became progressively smaller and finally presented irregular undulations resembling coarse ventricular fibrillation. After a few minutes the baseline was virtually at a standstill and the patient died. Postmortem examination showed chronic rheumatic mitral and aortic valvulitis with superimposed subacute bacterial endocarditis, acute myocarditis and pericarditis and focal embolic glomerulonephritis.

**Fig. 4.** Case 1. Terminal tracings shown in order in which taken. The first four strips show bizarre complexes with slow rate (66 in lead II) and irregular rhythm. Portions of the fourth and sixth strips show ventricular fibrillation. The final strip shows ventricular standstill.

**Case 2. Terminal mechanism in potassium intoxication: “ventricular flutter” and ventricular standstill.** J. Z., PBBH #68988, a 32 year old man, was admitted because of oliguria, melitturia and jaundice complicating excision of a parotid tumor performed six days previously at another hospital. Examination showed jaundice, slight generalized abdominal tenderness, a palpable liver, clouding of the sensorium and a large subconjunctival hemorrhage. Electrocardiograms showed tall pointed T waves characteristic of hyperkalemia but there were no physical signs corresponding to this finding. The serum potassium level was 7.4 and the serum sodium 130 mEq. per L., the nonprotein nitrogen 275 mg. per cent, total protein 5.7 Gm. per cent and serum bilirubin 1.32 mg. During the next three days until the patient’s death, a number of different treatments were exhibited and electrocardiograms were taken frequently, but in spite of temporary remissions, he went downhill rapidly. Necropsy showed lower nephron nephrosis, severe acute pulmonary edema, a normal heart and petechial hemorrhages in the bowel (“uremic colitis”).

Figure 5 illustrates serial electrocardiograms (lead II) taken during the 15 minute period preceding death. The first three (short) strips show progressive disintegration of the ventricular complex with prolongation of the QRS complex from 0.36 to 0.40 second and of the Q-T interval to 0.18 second. In the first long strip there is recorded, following a long pause, a series of oscillations with alternating tall and smaller peaks. The crude resemblance of each pair of peaks to the ventricular complexes recorded earlier suggests that they correspond respectively to the initial (depolarization) and final (repolarization) deflections. The absence of an isoelectric interval between the complexes and their over-all contour are reminiscent of the pattern of auricular flutter. This phenomenon continues through the next two (continuous) strips but the rate increases and the smaller peaks become less and less conspicuous and finally vanish so that an appearance was eventually recorded much more nearly like that of figure 2D of the preceding case. The fourth long strip, recorded less than a minute later, shows a flat plateau interrupted irregularly by broad sinusoidal troughs. The four long strips thus far recorded can be regarded as perhaps manifesting different variations of so-called “ventricular flutter.” In the following strip (8:53:48) a period of ventricular standstill lasting 5.6 seconds is recorded between two of the same type of disorganized sinusoidal ventricular complexes. The next strip (8:54:42) followed one minute 24 seconds of ventricular standstill with a smooth baseline. The progressive changes from larger, relatively regular and smoother undulations to smaller, coarser and quite irregular undulations are clearly shown in the next three strips which are continuous with this. Whether the last of these tracings represents ventricular standstill or fibrillation is difficult to say; if it is standstill, the waviness of the baseline is in marked contrast to the smoothness of the baseline recorded at 8:53:48. The complexes of the final strip, which followed four minutes and nine seconds of asystole with the same type of wavering baseline just described, resembled “monophasic action currents” with relatively rapid upward deflections and slow, smooth, rounded returning deflections. This series of beats, not entirely reproduced, lasted 18 seconds, successive ventricular deflections showing a progressive rounding off until the paroxysm ended abruptly with ventricular standstill. Occasionally monophasic ventricular complexes, singly
or in pairs, were recorded thereafter, but soon became less and less frequent and finally failed to appear.

cases, the operation of anoxia through the intermediation of electrolytic changes is an open field for investigation.

![Image of tracings]

**Fig. 5.** Case 2. Terminal mechanism in potassium intoxication. Complete set of tracings completed at 8:50 a.m. was characteristic of advanced potassium intoxication with auricular standstill, pronounced intraventricular block, bradycardia, irregular ventricular rhythm and pointed T waves in the precordial leads. Serial recordings of lead II are here illustrated showing possible variations of "ventricular flutter" in the first four long strips, ventricular standstill in the fifth (8:53:48) and in the beginning of the final (9:04:15) strips, and a wavering baseline in the next to the last strip.

Although, since these were terminal tracings, the role of anoxia cannot be eliminated, it should be emphasized that the serum potassium level on the day of death was 10 mEq. per L. Indeed, in certain cases, the operation of anoxia through the intermediation of electrolytic changes is an open field for investigation.

**Case 3.** Auricular fibrillation and idioventricular rhythm in potassium intoxication. B. E., PBBH #5B345, a 68 year old man, was admitted to the hospital on June 29, 1949, because of a hemolytic
reaction and renal shutdown following a transurethral prostatic resection. A detailed description of the clinical, chemical and electrocardiographic observations is presented in our other paper; for present purposes the sequence of changes recorded in lead V6 is reviewed. Figure 6A, recorded shortly after admission, showed bizarre broad QRS complexes occurring at the rate of 136 beats to the minute. P waves could not be recognized. The ventricular rhythm was regular. At first sight the strip had the appearance of ventricular tachycardia. However, in ventricular tachycardia the rhythm is generally slightly irregular and abrupt in onset. This diagnosis is not favored here because the rate increased gradually rather than suddenly and the ventricular complexes had a similar appearance when the rate was slower.

Figure 6B was recorded after the patient received 50 Gm. of glucose and 25 units of insulin by vein. Two important developments were noted: the QRS shortened and the rhythm became grossly irregular. In other words, the mechanism seemed to improve in one regard and become worse in another. With further increments of glucose and insulin (total glucose 100 Gm., insulin 50 units) (fig. 6C) there was further improvement in the ventricular complexes (clearer delineation of the S-T segments, smaller T waves and a still shorter QRS interval) but the arrhythmia persisted. It was not until after hemodialysis that the electrocardiogram became normal with regular sinus rhythm (fig. 6D).

The observation that the electrocardiogram apparently became worse in one respect (the development of arrhythmia) while improving in another (shortening of the QRS complex) during therapy which decreases the degree of hyperkalemia, is of considerable interest. It suggests that the regression of the tissue changes associated with hyperkalemia may be spotty, some islands of myocardial tissue recovering their irritability before others. If this conception were valid the relative concentration of potassium in the auriculoventricular node and bundle, on the one hand, and in the ventricular pacemaker, on the other, might determine whether or not the latter might be “released.” However, the fact that the ventricular complexes were of unchanging form is at some variance with the existence of an “escape” mechanism.

An explanation for this series of changes in rhythm, more consonant with current electrocardiographic teaching, would be that figure 6A represents idioventricular rhythm with either complete auriculoventricular asystole or auricular fibrillation* (fibrillation waves invisible) and that figure 6B represents either (1) the return of auricular fibrillation with irregular ventricular rhythm or (2) the persistence of auricular fibrillation with the subsidence of idioventricular rhythm and the resumption of some degree of auriculoventricular conduction*; and that figure 6D represents the return of sinoauricular rhythm.

Case 4 Premature ventricular beats, auricular fibrillation: U waves during subsiding hyperkalemia. K.B., PBBH 65546, a 35 year old housewife, was admitted to the hospital with a history of oliguria of eight days' duration which followed delivery of a child nine days before admission. In this case also, more detailed clinical, chemical and electrocardiographic data are presented in the parallel study; in the present communication attention is focused

* This explanation has a pharmacologic parallel in digitalis intoxication. The inception of a regular idioventricular rhythm superimposed upon pre-existent and persistent auricular fibrillation is generally regarded as an advanced toxic effect of digitalis.
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The initial tracings taken at 11:45 (fig. 7A) before treatment, showed typical changes of potassium intoxication. At this time the serum sodium level was 102 and the serum potassium 8.8 mEq. per L. and the patient was in coma. The initial tracings taken at 11:45 (fig. 7A) before treatment, showed typical changes of potassium intoxication. At this time the serum sodium level was 102 and the serum potassium 8.8 mEq. per L. and the patient was in coma. In lead V$_5$ auricular activity was not demonstrable. The dominant rhythm was slightly irregular; this was interrupted by a short run of rapid beats. The fourth and sixth complexes in this strip were ventricular premature beats. The intervening (fifth) beat was of the usual form seen in this lead but it showed some aberration. In lead V$_6$ taken immediately thereafter, another period of rapid heart action was recorded. This began with the third beat in the strip which was of approximately normal form showing a slight alteration, probably an artefact. The next two beats were premature and almost of the same form as the beats indigenous to this lead. From their resemblance to the usual complexes these beats must have arisen near the auriculoventricular node. The sixth complex was of the usual form for this lead and the seventh a premature ventricular beat. Premature ventricular beats, isolated or arranged in similar grouping, were in our experience recorded in only one other case of potassium intoxication.

Figure 7B taken of V$_6$ at 12:15, shortly after sodium bicarbonate therapy, when the sodium and potassium levels were 102 and 7.8 mEq. per L respectively and the patient was becoming responsive, showed the return of normal intraventricular conduction and the sporadic reappearance of broad low P waves and a long P-R interval. When P waves were absent the rhythm was slower (about 36 beats to the minute) and slightly irregular; when P waves were present the rhythm was regular and about
twice as fast (72 beats to the minute). This might be explained as due to alternating periods of normal sinus rhythm and auricular standstill. If this were true, however, one would expect the ventricular pacemaker to beat at a regular rhythm during the period of auricular standstill. Since the ventricular rhythm was irregular it seems more reasonable that

not yet recorded. It would be difficult to venture a precise definition of the arrhythmia present at this time but here again the most reasonable formulation would be alternation of auricular fibrillation and sinoauricular rhythm, occasionally arrhythmic. Sinus arrhythmia of the type described has been observed repeatedly in potassium intoxication. The same

this strip represents alternation of auricular fibrillation with a slow ventricular rate and short periods of normal sinus rhythm.

Figure 7C, showing leads II, III, aVR, aVF and V₅, recorded at 1:15 following calcium therapy, showed sporadic, low voltage P waves. Except in the last lead illustrated, the auricular waves, when present, showed arrhythmia, apparently sinus arrhythmia. And the P-R interval, though prolonged, was variable. In lead V₅ consistent sinoauricular activity was present and the P-R interval quite fixed. Thus the auricular and ventricular rhythms were regular at 75 beats to the minute. U waves were rhythm is illustrated also in figures 2 B, C, G, H and I. These observations suggest that either auricular fibrillation or sinus arrhythmia may account for the arrhythmias of supraventricular origin occurring during potassium intoxication. In other clinical conditions auricular fibrillation of recent onset is generally associated with coarse, easily recognizable fibrillation waves. Since such waves have not been recorded in cases of potassium intoxication reported as showing auricular fibrillation, the implicit or direct assumption has been made that in potassium intoxication fibrillation waves are not demonstrable. In view of the general decrease of all electrical activity

FIG. 8. Case 5. Electrocardiograms obtained from patient in congestive heart failure and probable pulmonary embolism when serum potassium was 5.8 and sodium 122 mEq. per L., showing interference and dissociation and characteristic changes of left ventricular enlargement. Auricular beats labelled C were conducted to the ventricles breaking up the idioventricular rhythm.
in the auricles in potassium intoxication, this assumption seems reasonable. This suggests that the experimental induction of auricular fibrillation in an animal previously rendered hyperkalemic might clarify this problem. That such a study would be difficult to evaluate is suggested by a related investigation carried out from a somewhat different point of view by Wiggers and co-workers. These authors emphasized that ventricular fibrillation developing following the infusion of potassium salts is quite distinct from ventricular fibrillation induced by faradic stimulation.

Figure 7D, taken at 4:45, an hour and a half after glucose-insulin therapy, when the serum potassium level was 7.3 mEq per L, revealed more clear-cut P waves but still showed a long P-R interval and sinus arrhythmia. This is most apparent in lead aVR. In the precordial leads tall pointed T waves and, for the first time, well marked upright U waves were recorded, especially in leads taken over the right ventricle. U waves have been observed during the hypokalemia which may occur following diabetic acidosis. We have observed U waves in about half of the tracings of patients with hyperkalemia and in most of those in whom the heart rate was slow enough to expose an interval between the T wave and the succeeding P wave or QRS complex adequate to permit the inscription of a U wave. In those cases with rapid rate, a U wave, though not visible, might have been obscured in the following P wave or QRS complex. Thus U waves may be present in hyperkalemia as well as hypokalemia and one cannot distinguish between these two extremes on the basis of the presence or absence of a U wave.

A subsequent tracing taken following the use of the artificial kidney was normal in every respect; U waves were still present.

Case 5. Interference and dissociation, left bundle branch block associated with hyperkalemia. H. H. V. PB 1B 402, a 49 year old man with calcific aortic stenosis and insufficiency, angina pectoris, syncopal attacks and chronic congestive heart failure, was admitted on May 4, 1949 because of thrombophlebitis and pulmonary embolism. Electrocardiograms on the following day (fig. 8) showed interference and dissociation and characteristic changes of left ventricular enlargement. At this time the serum sodium level was 122 mEq per L and the serum potassium 5.8 mEq per L. On the morning of May 7, the electrocardiogram (fig. 9) showed an irregular rhythm with broad P waves and changes very suggestive of potassium intoxication. In this instance, lead aVL and additional leads in the posterior axillary line and the midscapular line at the same horizontal level as V₆ (i.e., leads V₅, V₆) showed late intrinsicoid deflections. This change, though not altogether characteristic, suggested the existence of left bundle branch block. The blood serum at this time contained 120 mEq per L of sodium and 6.9 mEq per L of potassium. The patient died later that morning in acute pulmonary edema. Permission for a postmortem examination was not obtained.

This is the first instance in the present series in which suggestive evidence of left bundle branch block was recorded, and the only case in which interference and dissociation was associated with hyperkalemia. The relationship between this chemical change and the electrocardiographic appearance is problematic. We wish merely to record their coexistence.

Case 6. The sequence of peaked T waves, left bundle branch block and diffuse intraventricular block in
hyperkalemia. P. P., PBBH s P2473, a 46 year old taxi driver with tabes dorsalis, diabetes and chronic nephritis was admitted on January 4, 1950 because of uremia. Throughout a long hospital stay he went steadily downhill, in spite of a great deal of elaborate therapy, and died on February 18, 1950. Postmortem examination showed left ventricular hypertrophy, coronary atherosclerosis without infarction and branch block with peaked T waves but the QRS complex increased to 0.17 second and first degree auriculoventricular block was present (P-R interval 0.22 second). At this time the potassium level was the highest recorded in this patient (8.8 mEq. per L). In subsequent tracings normal auriculoventricular conduction was present with left bundle branch block.

![Fig. 10. Case 6. Normal initial set of tracings taken at the time of a previous admission for an infected finger. The second set, taken shortly after the final admission, shows tall, pointed T waves (see arrows) in leads V2 through V4. At this time the serum potassium level was 6.6 and the serum sodium 142 mEq. per L. The next two sets of tracings show left bundle branch block, apparently with superimposed peaked T waves. Numerous tracings obtained throughout his hospital stay resembled those recorded on January 10 but those obtained on February 10 showed first degree auriculoventricular block. (P-R interval 0.22 second) At this time the serum potassium level was 8.8, the serum sodium level 138 mEq. per L. The QRS interval increased from 0.13 second in the third set to 0.17 second in the final set of tracings, evidence of superimposed diffuse intraventricular block.]()

chronic passive congestion of the viscera. Microscopic examination of the kidneys showed chronic glomerulonephritis, chronic pyelonephritis and arteriosclerosis. The initial set of electrocardiograms (fig. 10) taken during a previous admission were normal. The second set of tracings recorded shortly after the present admission showed tall pointed T waves, characteristic of hyperkalemia. At this time the serum potassium level was 6.6 mEq. per L. The third set of tracings, taken five days later, showed left left bundle branch block (QRS 0.13 second) with normal auriculoventricular conduction. The T waves were still tall and pointed, perhaps more so than one usually sees in uncomplicated left bundle branch block due to other causes. The final set of tracings taken one month later still showed left bundle

An impulse in a bundle branch may be delayed (incomplete bundle branch block) or blocked (complete bundle branch block). Once blocked it cannot suffer a greater degree of block. The further prolongation of the QRS interval in this case cannot therefore be attributed to “more” left bundle branch block. It is necessary then to attribute this change to diffuse intraventricular block involving the remainder of the ventricular myocardium. Yet the sequence of events recorded here should remind us that if the changes of diffuse intraventricular block develop very rapidly the transition through an intermediate stage of bundle branch block could be missed.

This was the first instance in the present series in which left bundle branch block was clearly demon-
strated. It is possible that bundle branch block was present in other cases but its features may have been swamped out in the general impairment of intraventricular conduction, or overlooked because of an inadequate number of leads. We felt, however, that our findings in these cases showing a prolonged QRS duration were more in line with those of Finch and co-workers who considered that in potassium poisoning the defect in intraventricular conduction must be regarded as a more general one affecting the ventricle as a whole, myocardium proper and bundle branches alike.

**Discussion**

According to current teaching the surface of the cell, and more particularly of the myocardial cell, is polarized in the resting state, the charge upon the outer surface exceeding that on the inner surface. Among other factors, and perhaps most important of all, it is considered that the difference in potassium ion concentration between the outside and the inside of the membrane determines this difference in potential. If this normal differential is disturbed, as by painting a part of the surface of a nerve fiber, or of the epicardial surface of the entire heart, with potassium solution, that part of the nerve fiber or of the heart becomes partially or wholly incapable of responding to an electrical stimulus. The type of response is similar to that which develops if the same surface is injured mechanically, is cooled, or is deprived of its blood supply. It has been suggested that any of these procedures permits the migration of potassium ions from the inner to the outer surface of the cell, thus minimizing or eliminating the difference in potential across the cell membrane. By whatever means such a change has been produced, that portion of the surface which is less intensely polarized or which is no longer polarized, becomes less capable in the one case, or incapable in the latter, of responding to an electrical stimulus. Changes in the voltages of the deflections corresponding to depolarization and repolarization of the tissues in question are thereby produced. These considerations may explain the decrease in the voltage of the P wave and of the R wave observed in clinical potassium intoxication.

In addition to altering the magnitude of the electrical response of the heart muscle to the stimulating current in this way, potassium also slows the rate of conduction of the impulse in the myocardium. As a consequence, the P wave and the QRS complex are prolonged. Changes in the T wave could develop as “secondary” manifestations of the QRS changes or they might be “primary” and not accounted for on that basis. The prolongation of the Q-T interval characteristic of potassium intoxication could result from the prolongation of the QRS and/or T waves or from “primary” ischemic or ischemia-like changes. An evaluation of this problem by determination of the ventricular gradient in potassium poisoning is now in progress.

It has been shown that solution of potassium salts applied to the epicardial surface of the heart produced a “current of injury” so that an electrode in relation to the surface bathed with potassium records upward deviation of the RS-T segment. This is similar to the change produced by searing the surface with the electric cautery or by producing ischemia or infarction of the same area by ligating the coronary artery nourishing this region. Conversely injury to the subendocardial layers of the myocardium similarly damaged or injected with potassium solution produces, at an electrode in relation with the ventricular cavity, an elevation of the RS-T segment and a late deeply inverted T wave. At the same time an electrode in relation to the overlying epicardium records a ventricular complex the reverse of that just described, namely a depression of the RS-T segment, prolongation of the Q-T interval and a tall upright T wave. The unipolar right arm lead (lead V_R or aV_R) being generally in relation with the ventricular cavities, ordinarily records a downward QRS complex, the composite effect of the endocardial potentials of the right and left ventricles. If potassium produces an effect similar to that of injury at the endocardial surface of the ventricles, one would expect that in potassium intoxication one would find, in association with the depressed S-T segments in the precordial leads, elevation of the S-T segments at the endocardial aspect of the ventricle and thus in lead aV_R as well. A review of all cases in this study shows that such changes are indeed recorded. In potassium poisoning then, multiple
lead electrocardiography shows that the heart behaves electrically as if it were the site of a predominantly subendocardial injury. If the subendocardial layers of the ventricle were more vulnerable than the muscle layers remote from the endocardium to the effect of the potassium-rich blood, then the existence of these changes might be explained. This view has been anticipated by Wiggers, Theisen and Shaw, who felt that potassium produced depressed conduction first in the bundle branches and internal layers of the ventricle and subsequently in diverse portions of the myocardium. At the present time, however, this view must be regarded as possible but unproved.

In case 5 possible left bundle branch block was detected on the morning of the patient's death when the serum potassium level was 6.9 and the serum sodium level 120 mEq. per L. In case 6 clearcut left bundle branch block developed with the QRS duration lengthening from 0.13 to 0.17 second. Both of these patients showed sufficient prolongation of the QRS interval to demand the additional assumption of a profound degree of nonspecific intraventricular block. It is possible that if more extensive electrical exploration were made in all cases, more instances of bundle branch block would have been detected. The present observations are too limited to justify a statement as to whether a general delay in intraventricular conduction necessarily precedes the development of unmistakable evidences of bundle branch block or whether, as Wiggers and associates maintained, and as seems more likely, the bundle branches and subendocardial tissues are the initial sites of block. In any event, it seems quite clear that in the more advanced stages of potassium intoxication with general delay in conduction and without the coordinating effect of specialized conducting tissue, the human heart behaves electrically like the lower vertebrate heart, which is made up of striated cardiac muscle but which lacks specialized conducting tissue, or even like the smooth muscle heart of some of the lower invertebrates.

It has been emphasized above that in view of the uncertainty as to whether auricular activity actually persists in the more severe grades of hyperkalemia, one frequently cannot differentiate between auricular fibrillation and sinus arrhythmia. When one is uncertain as to the type of auricular rhythm, the type of ventricular rhythm is equally uncertain. It is then impossible to say whether ventricular complexes are conducted from the auricles or arise independently as "idioventricular" beats. For this reason we have found it necessary to present alternative explanations of the rhythms in some of the cases described above. In the future such cases deserve study with the esophageal or intracardiac electrode.

**Mechanism of Arrhythmias**

It is impossible to venture a definite decision as to whether these arrhythmias develop as a result of myocardial depression with "escape" of nondepressed areas of the heart or as the result of increased irritability of certain parts of the heart. Cases of ventricular escape (case 1) and of premature ventricular beats (case 4) were encountered in the present study. The escape can reasonably be attributed to primary depression; the explanation for the latter depends upon the conception held of the mechanism of ventricular premature beats. There is as yet no agreement upon this point. If one considers these to be due to reentry or to emergence of impulses from a parasystolic focus, primary depression might be the primary mechanism: if due to heightened activity of an ectopic pacemaker or to the development of a supernormal phase or of a heightened supernormal phase, increased excitability might be the mechanism. We believe, however, that the weight of evidence in this study is in favor of the hypothesis that potassium intoxication produces these arrhythmias as result of its depressive action.

It is held by some authorities that abnormal rhythms arising in the course of acute myocardial infarction may be "triggered" by local "currents of injury" dependent upon differences in the degree of polarization of contiguous areas of the myocardium. Similar local differences in the degree of potassium depression of the myocardium have been postulated. It is conceivable that such differences in the potential change across the cell membrane may initiate the abnormal normotopic and heterotropic rhythms.
which may develop in the course of potassium intoxication. It is even possible, in fact, that the abnormality in either condition involves a similar mechanism, namely local differences in surface ion (and particularly potassium ion) distribution. The relationship between these disturbances of impulse formation and impulse conduction is unknown; it seems reasonable, however, that some relationship must exist between the two.

Effect of Potassium through Anoxia and Nervous Influences

Potassium intoxication probably influences the heart and the electrocardiogram not merely through its direct myocardial effect but also through other, more complicated, and as yet even more vaguely understood mechanisms. Thus, impaired contractility of the heart may be associated with decrease in coronary perfusion and result in myocardial anoxia. This anoxia, acting directly or through changes in electrolytes in the myocardium, may be capable of producing profound electrocardiographic effects. Furthermore, there is evidence that nervous influences mediated through the sympathetic and parasympathetic divisions of the autonomic nervous system influence the development of abnormal cardiac rhythms. Increased vagal tone or sympathicomimetic drugs can predispose to or actually induce auricular fibrillation. Although the idea has been abandoned that potassium is actually the chemical agent causing ganglionic discharge at parasympathetic nerve endings, there is some evidence that movement of potassium ions may in some way be concerned with the release of acetylcholine. Potassium is also capable of stimulating sympathetic ganglions and initiating epinephrine discharge. Although epinephrine itself is probably not a fibrillatory drug it may under certain circumstances, such as light chloroform anesthesia, act in this way. It is apparent then that the influence of potassium upon the heart is a complicated one and depends, among other factors, upon myocardial anoxia and upon its effects on vagal and accelerator mechanisms as well as upon its direct action on heart muscle.

Potassium and “Cor Mortem”

One of the first two cases of potassium intoxication reported from this clinic was found in retrospect by a review of the “cor mortem” tracings in the electrocardiographic file. From a review of the literature and their own experience Stroud and Feil recently constructed the following composite summary of the terminal electrocardiographic sequence in individuals who did not die suddenly; “The initially rapid rate with sinus rhythm slows... There is prolongation of the auriculo-ventricular conduction time. Then excitation is initiated in the auriculo-ventricular node. Next auricular activity ceases as the ventricular pacemaker develops. At this time if many ectopic foci become active ventricular flutter and fibrillation may ensue. Then, either the rate slows and the heart stops, or the rate increases and again a flutter-fibrillation may occur... The QRS complex widens and is reduced in amplitude. The T waves become larger and, if inverted, become upright. Finally the QRS and T merge into a monophasic positive wave...” It is apparent at once that this is an apt description of the terminal sequences in experimental and clinical potassium intoxication. Although studies of blood potassium were not made, it is quite probable that in many of these terminal tracings published in the medical literature (for example, Stroud and Feil’s second case, one of carbon tetrachloride poisoning and uremia), potassium intoxication was the actual cause of the terminal rhythm. Although anoxia is probably of primary importance, we do not yet know whether similar mechanisms developing terminally in coronary artery disease or acute myocardial infarction are implemented, in one way or another, by alterations of extra- and/or intracellular potassium in the heart muscle.

The recent demonstrates of variation in the height of the T wave in association with changes within what is generally considered the normal range of potassium concentration is of considerable interest. These findings may explain some of the normal variations in the T wave as well as the extreme difficulty we have experienced in trying to decide whether the tall or suggestively peaked T waves seen in a
given tracing fall within or beyond the normal range.

**Summary**

Many cases of potassium intoxication develop a grossly irregular slow ventricular rhythm. At times this is associated with persistent but feeble electrical activity in the auricles and must be attributed to sinus arrhythmia. At other times electrical activity cannot be demonstrated in the auricles; it is believed that auricular fibrillation may exist in these cases. With increasing severity of potassium intoxication the rhythm may again become regular; this can be explained by the development of idioventricular (nodal) rhythm. In one patient interference and dissociation was recorded when the serum potassium level was elevated. In most cases hyperkalemia was associated with a diffuse slowing of intraventricular conduction; in one patient probable, and in another definite, left bundle branch block was demonstrated. First degree auriculoventricular block was commonly encountered but higher grades of auriculoventricular block could not be recognized because of disappearance of the P waves. U waves are commonly present in hyperkalemia.

Ectopic ventricular complexes occurring either as escape or premature beats were recorded singly or in paroxysms. The electrocardiographic appearance of "ventricular flutter" recorded in one patient with potassium intoxication changed to that characteristic of ventricular tachycardia during glucose-insulin therapy and before the tracings, on continuation of the same therapy, reverted to a more normal appearance. This patient later died of ventricular fibrillation. It is not known whether these ectopic rhythms develop as a result of increased or decreased myocardial excitability, though the data in this study seem more compatible with the latter view. In hyperkalemia the heart behaves electrically (elevated S-T in lead aVR; depressed S-T in the precordial and in some of the limb leads) as if the potassium-rich blood exerts a greater "injury" effect upon the subendocardial fibers than is exerted elsewhere in the heart.

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