R. J. KERNOHAN, M.D., F.R.C.P., F.R.C.P.(I), D.P.H., D.C.H., 1919-75
(By courtesy of Van Buren, and Mrs. R. J. Kernohan)
A CASE OF THE CARDIO-AUDITORY SYNDROME (LONG QT INTERVAL AND PROFOUND DEAFNESS) DIAGNOSED IN THE PERINATAL PERIOD AND KEPT UNDER SURVEILLANCE FOR TWO YEARS *

by

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PROLOGUE

I first met Bert Kernohan in the spring of 1964. He was keen to enrol the help of my senior colleague John Pemberton (then Professor of Social and Preventive Medicine) with some work he was planning in the Ballymena area into the aetiology of ischaemic heart disease and the early detection (in school-children) of hypertension with a view to an interventionist study: the general concern of the profession allied to his own developing interest stimulated the former; the incrimination of hypertension in ischaemic heart disease and the recent marketing of suitable corrective drugs, mainly beta-adrenergic blocking agents, focussed his attention on the latter. I fancy Pemberton was somewhat sceptical; he couldn’t believe that a physician remote from a teaching centre and running a busy consultant practice could organise and supervise the necessary large-scale studies on these complex subjects which were at that time attracting some of the best brains and the heaviest funding in the medical world. But he was sympathetic — he was after all the biographer and former assistant of Will Pickles (Pemberton, 1970), the country doctor who was an ideal prototype for Samuel Smiles who had added significantly to our knowledge of inter alia infectious hepatitis and Bornholm disease from observations made in his single-handed practice in Wensleydale. He asked me if I knew Kernohan: Bert and had not then met, but I knew his reputation by the tongue of good report — a busy and esteemed physician with a first-rate mind (he had graduated in 1941 with first-class honours and in three post-RAMC years had collected the MD, MRCP, MRCPI, DPH and DCH(Eng.) ) and who had published widely, remarkable for one unconnected with a major teaching hospital or medical school. When Bert arrived Pemberton and myself were quickly convinced by

*This material comprised much of the first Kernohan Memorial Lecture given at the Postgraduate Centre, Waveney Hospital, on 18th October 1977 by one of us (P.F.) who is, however, solely responsible for the Prologue.
his knowledge, drive, and above all sheer enthusiasm, and but for the facts that Pemberton was already conducting a study of his own into deaths from coronary disease in Belfast (which became one of the important pioneer epidemiological works in this field in the 1960s (McNeill and Pemberton, 1968)) and the notorious unreliability of blood pressure readings “in the field”, he would I believe have been pleased to co-operate in the proposed Ballymena studies. Though he had not received tangible help, only encouragement, Bert and I at once became friends. About this time two articles of mine on certain cardiac conduction anomalies and their genesis were published (Fraser et al., 1964a,b) and from that time we added a common interest to our friendship and we used to sit and and talk about electrophysiology of the heart, a subject about which I knew, and know, very little, and he knew even then quite a lot and came to know even more. I hope I don’t delude myself too outrageously in believing that Bert’s increasing interest in cardiac dysrhythmias (Kernohan, 1966a,b; Grant et al., 1966) owes something to those days.

In 1971 I became Dean of the Faculty of Medicine: Bert’s congratulatory note was among the first I received. He was then as he remained post-graduate, and to some extent medical, Pooh-Bah at the Waveney Hospital but unlike his fictional prototype he was courageously making a great success of his many activities including the postgraduate centre (Biggart and Kernohan, 1974), and when the hospital came to be more closely connected with Queen’s in the developing undergraduate teaching and attachment programmes Bert became a member of the University Faculty of Medicine and until his death rarely missed a meeting. In 1973 he was appointed Clinical Lecturer and Examiner in Medicine (for final MB) and discharged his duties with customary skill and gusto and a certain modest regard for convention. He contributed frequently and constructively to Faculty business, took a deep interest of all aspects of medical education, and I believe cherished these links with his old University and Medical School as deeply as he cherished his distinction in being examiner, and latterly senior examiner, for the Royal College of Physicians of Ireland.

About this time Bert helped me in a more personal way: he asked me if I wished to be proposed for ad eundem Fellowship of the Dublin College. The occasion of the invitation, if not his invitation itself, was of some moment. We were staying overnight in Dublin in Buswell’s Hotel in Molesworth Street and this, as it turned out, gave us a ringside seat for the great Sinn Fein march on the Dail to protest against the emergency anti-terrorist measures which the Fianna Fail government of 1972 was introducing in its dying days. The crucial debate and division were to take place that very evening and trouble was widely forecast: even an attack on Leinster House itself was only ridiculed by the over-confident or the under-informed! Molesworth Street was soon packed with a lusty placard-bearing and shouting mob which rushed in from Dawson Street and was only stopped by a massive police barricade which stretched from the hotel to, appropriately perhaps, the headquarters of the Masonic Order in Ireland (Irish Constitution)! Speeches were made from the back of a slogan-bedecked lorry by Bernadette Devlin and colleagues, and things looked ugly for a time, but eventually the crowd was part broken-up by the Garda, part dispersed, and

116
left Molesworth Street, Leinster House, Buswell's Hotel, and the State intact. (Earlier, while parking my car in Merrion Square, the street lights were extinguished and a dozen or so tenders of fully-accoutred troops passed my car and entered Leinster House from the rear, a reminder of how seriously Dublin at that time took the Sinn Fein threat!) This vision of Götterdämmerung seemed an appropriate backdrop for my entry to this new stage in my career, and so I agreed to Bert's suggestion. He at once went ahead, successfully as it turned out. He then even more daringly proposed my name to the Censors of the London College for election to their Membership under bye-law 117 — election through the evidence of published work. (He spared my blushes from likely failure by keeping this initiative to himself!) Surprisingly he was again successful and he attended the ceremony in London making the journey for this sole purpose, a gesture completely typical of this warm-hearted man. All this he did through altruism and genuine friendship: he sought from me no favour for I had none to give; he was not advancing a protégé for I was not that; he was not acting on my wink or nod because, although I greatly respect and enjoy my connections with these great Colleges, I am immodest enough to believe that my career, such as it was, had not suffered from their lack. Bert also invited me to speak at post-graduate meetings and symposia and we always kept in touch on unusual cases of cardiac arrhythmias, and during all this time I came to esteem him highly for his wide knowledge, his compassion, his vitality, and above all for his complete commitment to his profession and to those he served. By force of knowledge, energy, character, and personality he dominated his local scene to a degree that, without disrespect to his colleagues, Bert and Waveney medicine became almost synonymous. I last saw him a month before he died: typically he had driven from Ballymena to my house late one evening after a full day's work to tell me some follow-up facts of a case we had reported (Kernohan and Froggatt, 1974). His sudden and untimely death removed an outstanding doctor, one of Ulster's best physicians and a man I was proud to call my friend.

A lecturer in a memorial series often tries to assess the place his subject occupied in his discipline and his profession. I think it is too proximal to Bert's death to be able to present a balanced perspective: some later lecturer will I hope attempt the task. Furthermore, though Bert published regularly and, for a busy physician, also extensively, his greatest legacies are outside the covers of journals — the strength and reputation of the Waveney, its postgraduate centre, and the admiration and thanks of thousands of patients who worshipped him. Bert's major clinical and research interest was cardiology and I hope I may adequately serve his memory if I offer as a personal Festschrift a hitherto unreported case of a syndrome on which he and I had previously published (Kernohan and Froggatt, 1974), about which he was intensely interested, and which a decade before I had helped to delineate (Fraser et al, 1964a,b) and the unusual aspects of which had I believe done something to stimulate Bert's interest in cardiac dysrhythmias all those years ago. Much of the clinical work in this case is due to my colleague, Dr. Jennifer Adgey, consultant cardiologist at the Royal Victoria Hospital, who appropriately appears as joint author.
THE HEREDITARY QT PROLONGATION SYNDROMES

In the 1950s a brief case abstract (Möllner, 1957) and two detailed reports (Jervell and Lange-Nielsen, 1957; Levine and Woodworth, 1958) were published from Scandinavia and America describing in all six children (in three sibships) who were severely deaf from infancy and had had recurrent syncopal attacks during which four had died suddenly. This combination of profound "congenital" deafness, syncope, and sudden death in a child had only once been previously reported — by Meissner (1856) in anecdotal form in a lengthy book (Fraser et al, 1964(b). The electrocardiogram (ECG) was unique and characterised by a grossly prolonged QT (or QU) interval and certain TU wave changes (mainly biphasic or alternating polarity, and high voltage on the unipolar chest leads) most especially following emotional disturbance, and (frequently) sinus bradycardia. The clinical picture is fully reviewed by Fraser et al (1964a) and Jervell (1971). Later studies (e.g., Jervell and Sivertssen, 1967; Olley and Fowler, 1970) showed the syncope (and sudden death) to be due to ventricular fibrillation or asystole: the prolonged QT interval whatever its cause (it was then assumed to be due to a cellular biochemical anomaly), indicates a myocardium unusually vulnerable to minor supraventricular aberrant rhythms and dysrhythmia-triggering mechanisms generally which would be harmless in a normal heart. Associated and unusual pathology in the blood vessels and neural elements in the sinus node (Fraser et al, 1964a) and inner ear (Friedmann et al, 1966, 1968) of equivocal significance were also reported. The condition segregated in families as an autosomal recessive trait (Fraser et al, 1964b). Six years after the first reports two other families were described with affected members displaying all the above features except that they heard normally (Romano et al, 1963; Ward, 1964), the pattern of inheritance being autosomal dominant with varying expression. Since then well over 100 families have been described world-wide of either the rarer cardio-auditory syndrome or the commoner Romano-Ward syndrome (see Schwartz et al (1975) for review) and further cases are regularly documented. Research has mainly aimed at (a) delineating the syndromes and searching for any genetic connection, or linkage with other identifiable genes, (b) elucidating the cause of the QT prolongation and TU changes with a view to rational treatment or correction, (c) identifying the mechanisms triggering and self-limiting the potentially lethal ventricular arrhythmias, (d) introducing an effective therapeutic regimen to reduce the number and length of the attacks of syncope and hence reduce mortality, (e) instigating basic biochemical and pathophysiological research into possible underlying mechanisms and the mode of gene action which produces the pleotropic stigmata of the syndromes, and (f) investigating whether these or any associated syndromes could account for a significant proportion of cases of unexplained death in childhood or "cot death" (Froggatt and James, 1973).

This paper describes a case of the cardio-auditory syndrome which exhibits some important features not previously described and which provides information under (a), (b), (d) and (f) above. It has been referred to briefly in another context (Froggatt and James, 1973). Discussion and recent reviews of these syndromes are in Schwartz et al (1975) and Vincent et al (1974a).
CASE REPORT

Gerard S. was born in the Royal Maternity on 18th May, 1971. At 37 weeks maturity an amniocentesis had been carried out (because of maternal Rhesus iso-immunisation) during which foetal bradycardia, taken as indicating foetal distress, was noted and a lower section was performed. Birth weight was 2.6kg; Apgar score 5; heart rate 160 per min; no cardiac murmurs; haemoglobin 13.2 g/dl; liver and spleen enlarged; direct Coombs' test positive. There were no other significant findings. At age four days exchange transfusion was initiated. Bilirubin was 350 μmol/l (20.4 mg/100 ml); heart rate 116 per min. After 30 mins (with 135 ml of blood withdrawn and 125 ml replaced) the child became cyanosed and “quiet”. Heart rate was 80 per min and noted as “irregular”. Exchange transfusion was stopped, the clinical picture improved but bradycardia persisted at 80-100 per min and an ECG was taken. This showed a prolonged QT interval (Fig. 1)* and was provisionally attributed to

* The parameters and notation used in the text and figure captions with reference to measurement of the QT interval are explained in Appendix B.
electrolyte imbalance: potassium was 5.60 mmol/l (=Eq/l), calcium 1.62 mmol/l (6.50 mg/100 ml), magnesium 0.70 mmol/l (1.65 mg/100 ml), and bilirubin 217 μmol/l (12.70 mg/100 ml). Calcium gluconate and magnesium sulphate improved the electrolyte picture and a second exchange transfusion was successfully completed. Four days later blood electrolytes were considered normal (particularly: potassium was 5.80 mmol/l and calcium 2.08 mmol/l) but the QT prolongation and TU changes persisted. The child was discharged on 31st May and the paediatric registrar (the late Dr. Cynthia Steele) referred the case to one of us (P.F.) as possibly a QT prolongation syndrome. On 7th July the child was found to be totally unresponsive to sound and a provisional diagnosis of the cardio-auditory syndrome was made.

First admission. This was on 2nd August 1971 to the Cardiac Unit, Royal Victoria Hospital (AAJA). Examination showed an alert child of normal-for-age physique. Heart rate was 120 per min and there was an ejection systolic murmur at the left sternal edge. The ECG was as previously with characteristic TU wave changes now marked (Fig. 2). Results of all the other extensive range of special tests and investigations were unremarkable. Continuous ECG oscilloscope monitoring with hourly print-outs was carried out for one month and disclosed permanent though variable QT prolongation and aberrant TU waves which characterise these syndromes, several short episodes of self-terminating nodal bradycardia, and several single late cycle ventricular ectopics (see Froggatt and James, 1973, Figure 2). Sequential stellate ganglion blockade (with xylocaine) of the left and right ganglion as a trial therapeutic measure was performed. The results were equivocal: there was no important effect on the QT interval or TU appearance but neither was there an ipsilateral Horner’s. Repeat trial was postponed (see later). On the experience of Jervell and Lange-Nielsen (1957) and Jervell et al (1966) the patient was digitalised and, though remaining prolonged, a persistent shortening of the QT interval compared to previous tracings resulted (e.g. on 2nd September: RR = 0.480 sec, QTs = 0.344 sec, QTc = 0.284 sec; (QTc — QTs) = 0.060 sec (P = 0.001). (For explanation see Appendix B). It is impossible to say how much of this improvement was unequivocally due to the therapy since the QT interval in these syndromes is remarkably variable (see Appendix A), but the more favourable picture persisted and the child was discharged on digitalis on 11th September, 1971. Frequent ECGs over the next 15 months showed maintenance of the digitalised, seemingly improved, pattern. In October 1971, aged 5 months, while taking digitalis, the child had his first serious syncopal attack characteristically while annoyed at being constrained at play. It followed the classic pattern of “severe” attacks described by e.g., Fraser et al (1964a) and Jervell (1971). In April 1972 he had a second similar one after a tantrum, and in September a third. During all this time he attended as an outpatient for check assessments and was judged to be regularly taking the medication.

First re-admission. This was on 23rd January 1973. Continuous ECG monitoring was re-commenced, digoxin was discontinued, and assessment of other relevant cardio-active drugs which had been previously described as efficacious in these syndromes was initiated viz sodium diphenylhydantoin (Dilantin;
Epanutin) as a single intravenous bolus of 36 mg; isoprenaline (or isoproterenol) (Saventrine) 5 mg qid for 3 days; and practolol (Eraldin) 10 mg qid. Dilantin and Eraldin, but not Saventrine, decreased the degree of QT prolongation and were later therapeutically used. (The assessment of these drugs is confounded by the often marked variation in the QT prolongation and TU complex changes from one time to another which occur in this syndrome necessitating detailed statistical analysis to isolate any drug effect. This is explained in Appendix A and illustrated in Fig 3). During the insertion of the intravenous cannula into the child’s arm for Dilantin injection he became very distressed, the QT interval elongated further and the T wave (precordial monitor lead) became prominent.
and inverted, and ventricular tachycardia and fibrillation (VF) ensued which was terminated by a "precordial thump" to the lower end of the sternum. In all, five such episodes of VF were documented: each was terminated in the same way (see later), Sinus rhythm returning usually after several beats of AV nodal rhythms (Figs. 4 and 5). Of the drugs therapeutically tested Eraldin had the most beneficial effect, though not as marked on the ECG as was digitalis, and the patient was discharged on 14th February on 10 mg qid. The parents were instructed how to thump the lower end of the sternum during a syncopal attack. The child was regularly reviewed and the Eraldin reduced to 10 mg tid because of complaints of "staggering" and "dullness". Audiogram confirmed severe bilateral perceptive deafness most marked in the higher tones. No further attacks were noted until 7th September when the child, now 28 months old, had a severe one and another three days later. The mother thought her "chest thumping" had stopped the second and possibly also the first.

Second re-admission. This was on 11th September. Continuous ECG monitoring was recommenced and Eraldin discontinued. On 28th September a left cervical sympathetic block at the level C6/C7 was effected using xylocaine. The following day he had a further episode of VF immediately preceded by R on T ectopics.
Fig. 4: Gerard S. (31st January, 1973). Note the run of ventricular tachyarrhythmia which reverted after a precordial “thump” (arrowed in third strip).

Fig. 5: Gerard S. (29th September, 1973). An episode of unequivocal ventricular fibrillation terminated by a precordial “thump” (arrowed on second strip).
This was terminated by a chest thump. On 1st October a right block (as above) was carried out. The results of these two blocks are in Figs 6 and 7: they are discussed in detail later but they appeared to effect a dramatic improvement in the ECG picture both on the length of the QT interval and on the TU complex.

On 3rd October a self-terminating episode of ventricular flutter was recorded,

![ECG tracings](image)

**Fig. 6** Gerard S.: Left stellate ganglion blockade (28th September, 1973). The top tracing (lead II) was recorded several minutes before blockade; the lower tracing 11 minutes after the start of blockade procedure and at the appearance of an ocular Horner’s. Note improvement in the ECG picture, post-blockade readings being (10 complexes): \(RR = 0.71 \text{ secs.}, \quad QT_c = 0.44, \quad QT_e = 0.33\), and \((QT_e - QT_c)\) now 0.11 secs. \((P < 0.001)\).

but there were no further attacks and the patient was discharged on 7th October on Dilantin, digoxin and Nacton to be re-admitted a week later for permanent cervical sympathetic block. Unfortunately on 9th October he had a further syncopal attack at home which proved refractory to parents’ precordial “thumping”. A post-mortem was not obtained.

*Family information.* The patient was the younger of two children (1F; 1M) born to healthy unrelated parents. Information covering kinships up to the third degree gave no history of syncope, fits, significant deafness, or unexplained or untimely sudden death. Audiograms on parents showed, for the father, bilateral loss up to 30 db at 4000-8000 Hz, and for the mother, left unilateral loss up to 55 db at 8000 Hz. Using Ljung’s (1949) formula for estimating \(QT_e\) in adults, ECGs of first-degree relatives of proband (mother, father, sister) were normal. Blood grouping (ABO, Rhesus, K, k, Kp^a, Fy^a, Jk^a, Le^a, MNS, Pi, Di^a) did not
discredit the suggestion of Friedmann et al (1968) of possible close linkage of the determinant gene with the cde allele though the Cw allele, segregating in two other Northern Ireland families containing members with this syndrome (Friedmann et al, 1968) was not identified.

DISCUSSION

This case of the cardio-auditory syndrome presents some unusual or previously unreported features of therapeutic value, as follows.

Early diagnosis

In this syndrome the first syncopal attack usually occurs in childhood but rarely as early (5 months of age) as was the case in this patient (of the 203 cases of the long QT syndromes collected by Schwartz et al (1975) only six had attacks recorded so young); and diagnosis has been made in only four patients prior to the first attack of syncope — all were close relatives of probands and investigated routinely (Schwartz et al, 1975). Our patient is only the second child
reported in which the cardiac anomaly has been demonstrated in the perinatal period (first week of life) and the first to be diagnosed so early: the other (Langslet and Sorland, 1975) had an ECG taken two hours after birth because of foetal cardiac distress during labour though the significance of the documented abnormality was not recognised at the time. The presence of the cardiac anomaly at birth confirms what was previously only speculation, is of embryological and developmental importance, and provides a basis for postulating that the QT prolongation syndromes can contribute to infant mortality over its full age range (birth to one year) and possibly also to stillbirths and foetal loss.

**Therapy**

This is aimed at (a) decreasing the myocardial vulnerability by shortening the (prolonged) QT interval and stabilising the TU complex, (b) reducing the number and severity of VF-triggering arrhythmias (premature and ectopic beats, etc), (c) reducing those factors known to enhance myocardial vulnerability and VF-triggering arrhythmias in these conditions e.g., fright, emotional stress, severe physical exertion, water immersion as in swimming, and (d) terminating, as an emergency, any potentially lethal ventricular dysrhythmia which arises. New evidence is provided here on (a) and (d), as follows.

**Stellate ganglion block.** Evidence, both hypothetical and experimental, has recently accumulated to suggest that the conduction disturbance in the long QT syndromes may be due to asymmetrical cardiac sympathetic innervation or imbalance rather than to metabolic disturbance at the cellular level *per se*. (i) Most victims have their attacks of syncope during periods of emotional or physical stress, or bathing, when neural influences will be marked and these have been shown also to worsen their ECG picture (e.g., Fraser *et al.*, 1964a, Figure 11). (ii) Postmortem cardiac anomalies — focal neuritis and neural degeneration within the sinus node, AV node, bundle of His, and ventricular myocardium — are concentrated in cardiac neurological tissue and have been accepted as determinants of, or at least correlates with, the clinical cardiological findings (James, Froggatt, *et al.*, 1978). (iii) Experimentation has demonstrated that asymmetrical sympathetic neural control of the heart may cause anomalies in myocardial repolarisation (Yanowitz, *et al.*, 1966; Abildskov, 1972) and left side sympathetic stimulation, or right side block, produces ventricular tachyarrhythmias including VF in certain instances particularly with a damaged or vulnerable myocardium (see Schwartz *et al.* (1975) for review). (iv) Beta-adrenergic blockade has had a putative efficacy in alleviating symptoms (Schwartz *et al.*, 1975). (v) Atrial pacing studies in some cases show QT shortening without T wave inversion as in normal subjects (Roy *et al.*, 1976). (vi) T wave polarity alternation, common in this syndrome and marked in the present case, can also be obtained by sequential unilateral stellate ganglion stimulation (Schwartz and Malliani, 1975). (vii) Cerebrovascular accident and central nervous system disease may produce lengthening of the QT interval and large T waves (Burch *et al.*, 1954; Hugenholtz, 1963). (viii) Direct interference with the existing cardiac neurological control in
QT prolongation syndromes affects the electrical conduction picture: thus several authors have demonstrated QT shortening in the Romano-Ward syndrome (prolonged QT interval without deafness) by stellate ganglion pharmacologic blockade and/or surgical ablation either of the left side (Moss and McDonald, 1971; Schwartz and Malliani, 1975), the right side (Ramon et al, 1972), or after both separately (Vincent et al, 1974b), though the longer-term persistence of the improvement is not yet established (Moss, 1973; Schwartz et al, 1975); others have found no change (Dear, 1975; Curtiss et al, 1978); and in the case of Ratshin et al (1971) the QT prolongation was increased after both right and then left side blockade. In the present case, seemingly the first patient with the cardio-auditory syndrome to be so treated, both left and then right side blockade shortened the QT interval and normalised the TU complex (Figs. 6 and 7) but unfortunately the patient died before the planned unilateral surgical stellate ganglion ablation or functional destruction could be performed. The dramatic response to stellate blockade — which waned as the ganglion recovered — was more marked than with practolol therapy and, in the overall picture, at least as well marked as with digitalis, and although no final decision had been reached on which side to operate (the literature at the time was unhelpful in that Moss and McDonald's (1971) patient's QT interval improvement after left stellectomy later regressed and the patient of Ramon et al (1972), after right stellectomy, died within six months despite an initial favourable response) it seemed the treatment of choice. This finding further confirms the common pathogenesis in these two QT prolongation syndromes.

Precordial "thump pacing" and "thump version". Patients with QT prolongation syndromes have self-terminating episodes of cardiac arrest (mainly VF) which may be frequent. It is not known why any particular episode persists and proves fatal while others spontaneously revert. It is clearly advisable to terminate such an episode as an emergency procedure and with a minimum of trauma. Pennington et al (1970) first showed that "precordial thumps" could revert ventricular tacharrhythmia, as well as (more commonly) asystole, to sinus or AV nodal rhythm by evoking a premature depolarisation of a re-entry pathway. If necessary the procedure could be continued rhythmically as "thump pacing" and is less traumatic than external cardiac massage. One of us (AAJA) terminated several documented VF attacks in our patient by "thump version", the first time in these syndromes that this has been described (Figs. 4 and 5).

Association with sudden unexpected death in infancy

The perinatal diagnosis of our patient allowed us to monitor his progress over the first two years of life: this included the period (2-5 months) when sudden unexpected death in infancy ("cot death") is most frequent. Ever since an early communication (Fraser and Froggatt, 1966) the possibility has been considered that QT prolongation and related syndromes could comprise a significant proportion of the "cot death" entity: sudden and unexpected (or unexplained) death through cardiac arrest such as had been documented in these syndromes. Pioneer
work by James (1968) indicated a basis for theorising enhanced dysrhythmic potential mediated through certain physiological maturation processes in the cardiac conduction system during the first year of life and which could lead to lethal arrhythmias in normal hearts and, a fortiori, in a vulnerable myocardium such as in the QT prolongation syndromes, and in 1973 Froggatt and James (1973) developed the hypothesis fully. Since then it has attracted considerable attention both critical and supportive (Valdes-Dapena, 1973; Valdes-Dapena et al, 1973; Maron, et al, 1975; James, 1976; Froggatt, 1977), and Schwartz (1976) has even speculated that cardiac adrenergic imbalance may play a role in sudden infant death as it might do in producing QT prolongation. Crucial evidence on the hypothesis is missing, or by its nature unobtainable: one finding which would help is — do we observe, in the first year of life and particularly at 2-5 months pari passu with the histomorphological changes in the conduction system first described by James (1968), an increased incidence of potentially lethal cardiac dysrhythmias? If these do not exist in the QT prolongation syndromes they are unlikely to exist to any extent in infants generally. Until the present case no such ECG monitoring of a QT prolongation child had been carried out.

The findings are equivocal. During the peak “cot death” age group (2-5 months) the only rhythm anomalies recorded were runs of self-terminating nodal bradycardia and sporadic late cycle ventricular ectopics such as previously reported in immature infants (e.g., Church et al, 1967) and which did not lead to syncope. However, from the age of about five months attacks of VF occurred any of which could have been fatal; and this is still well within the “cot death” modal age of risk. The (seeming) immunity of the very young infant both to “cot death” and, in the QT prolongation syndromes, to syncope bears further investigation: one, no doubt of several common factors, is that cardiac sympathetic innervation normally does not reach full maturation until as late as six months of age (Hirsch, 1970). Our results leave the status of the cardiac conduction hypothesis in “cot death” more or less as before.

SUMMARY

This article describes a case of the cardio-auditory syndrome (QT prolongation and severe deafness), the first to be diagnosed in the perinatal period and kept under surveillance and ECG monitoring over two years which included the “cot death” modal age range (2-5 months). Attacks of ventricular fibrillation were recorded and these were terminated by a precordial “thump”, the first time the success of this measure has been documented in the (often self-limiting) episodes of VF in this syndrome. Assessment was made of the efficacy of sodium diphenylhydantoin, digitalis, practolol, isoprenaline, and unilateral stellate ganglion blockade, and the authors conclude that in this patient digitalis or stellate ganglion blockade seemed the treatments of choice. Unfortunately the patient died before unilateral stelllectomy could be performed. The findings add further information concerning the status of the cardiac conduction hypothesis in “cot death”.

128
APPENDIX A

Many claims have been made for the efficacy of various cardio-active drugs in the QT prolongation syndromes based on reduction in the number and severity of the syncopal attacks and/or improvement in the ECG picture, viz shortening of the QT interval and normalising of the TU complex. Both of these criteria are difficult to assess, the former because of the rarity (in statistical terms) of the syncopal attacks in most cases and the difficulty in adequate patient follow-up, and the latter because of the marked variation in relevant ECG parameters from time to time in the same patient which is a marked feature in these syndromes (Fig. 3) and which is often associated with emotion e.g., fear at time of drug administration, or physical state e.g., sleep. Furthermore, any improvement resulting from treatment is often undramatic — an added difficulty in assessment. In this study we measured the effect, primarily on the length of the QT interval, of digitalis, isoprenaline, practolol, and sodium diphenylhydantoin. Digitalis clearly and consistently shortened the QT interval; sodium diphenylhydantoin and practolol appeared to do so also but to a minor degree; and oral isoprenaline had no important effect. In the second instance, to judge whether any improvement was attributable to the drug or to some extraneous factor (as above) we proceeded as follows.

Ten consecutive sinus rhythm complexes from ECG tracings at five different times before therapy (50 readings in all) yielded measurements which were used to establish reliable averages, and estimates of within-subject and between-complex variation, for the subject’s QT and RR intervals. With practolol, 10 mg tid was administered orally and ten consecutive sinus rhythm complexes measured every six hours for 24 hours and then (at 10 mg qid) every six hours for four days. Regression and covariance analyses show a significant (P<0.001) shortening of the (prolonged) QT interval, independent of heart rate (RR interval) in its linear and quadratic form, compared to the pre-therapy level and unaffected by whether the subject was asleep or awake. Maximum improvement was from the third day. In absolute terms the improvement was modest but perhaps important though any benefit should be set against the other known effects of beta-adrenergic blocking which may a priori have a dysrhythmic potential in these patients, e.g., slower heart rate less responsive to adrenergic stimuli. With sodium diphenylhydantoin, a single bolus of 36 mg was administered intravenously with the subject sedated and again ten consecutive sinus rhythm complexes measured this time every 90 seconds for 15 minutes. Regression and covariance analyses as before again show a true shortening of the QT interval though more modest (P<0.01) than with practolol. The maximum effect was nine minutes after drug administration.

The independent effect of sleep — as a binary factor ‘asleep’/‘awake’ — was tested because of its importance as a risk factor in “cot death”, its role in further prolonging the QT interval in one other case described in Froggatt and James (1973), and its dysrhythmic role in other analogous conditions (Johanssen and Jorming, 1972; Wellens et al, 1972). Similar analyses as above with 22 time-
points two hours apart (10 sleep; 12 awake) showed no significant difference in QT interval length ascribable to being "asleep" or "awake".

The multi-factor analyses used in the above do not easily permit meaningful absolute measurements of pre- and post-drug QT intervals to be given. Complete results are available on request to one of us (P.F.).

APPENDIX B

Prolongation of the QT interval is clearly the crucial diagnostic discriminant in the QT prolongation syndromes: its accurate measurement and comparison with "normal" values are therefore important. In this paper the QT interval is measured from the start of the Q wave to the final return of the T wave to the isoelectric line, the average of at least five consecutive complexes being taken. This is designated QT₀ for the subject examined.

The length of QT varies with heart rate curvilinearly (rather than linearly) and in children this relationship varies with age and sex. To establish an appropriate "expected" value for QT (QTₑ) i.e., the value QT would 'expect' to take in a normal person for a particular heart rate and given age and sex, to compare with QT₀, it is necessary to standardise for these variables. Extensive studies by Fraser et al (1964b) established appropriate population regression equations, the one used here being

$$QTₑ = 0.132 + 0.388 (\text{RR}) - 0.157 (\text{RR}^2) + 0.0017 \text{ age}$$

where RR is the length of the cardiac cycle of the subject in seconds,

$$\text{RR}^2$$ is its square,

age is the age of the subject in years.

Comparison of QTₑ with QT₀ will establish the degree of QT₀ prolongation if any.

Fraser et al (1964b) also showed that normal theory was applicable and that the standard error (S.E.) of QTₑ was 0.02 seconds. This means that the extent of QT₀ prolongation can be expressed in conventional probability terms i.e., where (approximately)

$$(\text{QT₀} - \text{QTₑ}) > 0.04 \text{ secs, then } P < 0.05$$

,, $$(> 0.05 \text{ secs, then } P < 0.01$$

,, $$(> 0.06 \text{ secs, then } P < 0.001$$

In the case presented in this paper the degree of prolongation of QT in the untreated patient is extreme (e.g., Figs. 1 and 2) and requires no sophisticated statistics: the importance of accurate assessment is in judging the effect of therapy.
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