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Hereditary prolongation of QT interval

Bengt W. Johansson and Bengt Jorming
From the Heart Laboratory, Department of Medicine, and Department of Paediatrics, General Hospital, Malmö, Sweden

Two cases, a father and son, with prolongation of the QT interval without coexistent deafness, are described. Both had a typical history, with symptoms starting in childhood, of transient syncopal attacks, often triggered by strong emotional or physical stimuli, an abnormally prolonged QT interval, bizarre T waves, and normal laboratory values. In contrast to cases described previously, their attacks had a manifest daily rhythm which could not be explained by circadian laboratory examinations.

Both patients had attacks during which no pressure or pulse could be palpated. Ventricular fibrillation was observed on the electrocardiograms made during one of the patient's attacks. In the other patient, continuous electrocardiograms with the aid of a tape recorder disclosed attacks of asymptomatic ventricular tachyarrhythmia.

Both patients were initially thought to be epileptics and anticonvulsant drugs were administered without effect. However, adrenergic beta-receptor blocking agents reduced the incidence, intensity, and duration of attacks.

In 1957, Jervell and Lange-Nielsen described a new disease complex which has come to be known as the 'surdocardiac syndrome'. To date, 27 cases have been described (van Bruggen, Sebus, and van Heyst, 1969; Dupuis *et al.*, 1969; Fraser, Froggatt, and James, 1964a; Jervell and Lange-Nielsen, 1957; Jervell, Thingstad, and Endsjö, 1966; Jervell and Sivertssen, 1967; Lamy *et al.*, 1967; Levine and Woodworth, 1958; Lisker and Finkelstein, 1966; Sánchez Cascos, Sánchez-Harguindey, and De Rabago, 1969). The main characteristics are as follows: (1) attacks resembling angina pectoris and/or syncopal attacks and/or sudden death; (2) a prolonged QT interval in the electrocardiogram; (3) congenital neural deafness; and (4) familial incidence.

Several of the attacks were traced to ventricular tachycardia, ventricular fibrillation, or asystole (van Bruggen *et al.*, 1969; Jervell and Sivertssen, 1967; Olley and Fowler, 1970; Ward, 1964). No consistent macroscopical or microscopical changes were found in the cardiac muscle or valve apparatus of patients on whom necropsies were performed. Symptoms usually made their debut in childhood. Attacks were often triggered by emotional excitement or great physical exertion. The frequency of attacks varies from patient to patient and tends to decline with increasing age, as is the case with the prolonged QT interval. T waves are often bizarre, e.g. inverted, diphasic, and varying in amplitude and shape from one occasion to another. Mechanical systole is reported as being normal. As a rule other laboratory examinations are completely normal.

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In 1963, a syndrome was described which was apparently identical to this, but with normal hearing: a total of 31 such cases have been published (Barlow, Bosman, and Craig Cochrane, 1964; Gale *et al.*, 1970; Gamstorp, Nilsén, and Westling, 1964; Kallfelz, 1968; Romano, Gemme, and Pongiglione, 1963; Ward, 1964; Wennevold and Kringelbach, 1971). Inheritance in the surdo-cardiac syndrome is considered to be autosomally recessive (Fraser, Froggatt, and Murphy, 1964b) but appears to be autosomally dominant in the latter syndrome. There is much to suggest that both syndromes have the same genetic background (James, 1967).

Two cases, a father and son, with congenital prolongation of the QT interval without coexistent deafness, will be briefly described.

Case 1

A 36-year old man.

Hereditary background There is no definite information on attacks, congenital heart disease,

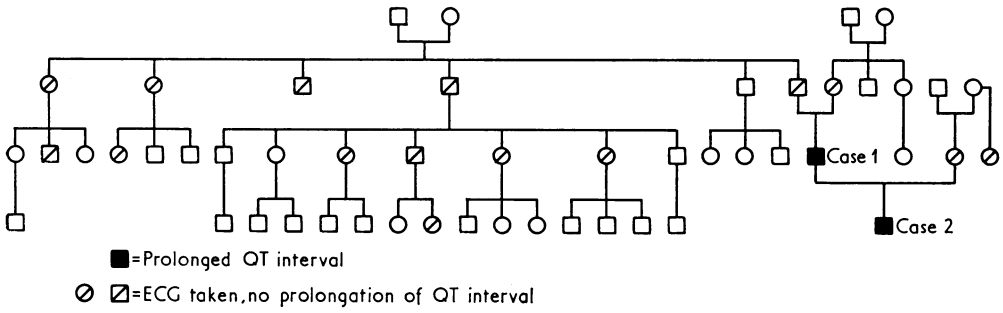


FIG. 1 *Pedigree of the family.*

or deafness in the family. However, there have been some phychoses or moderate mental disturbances. Only the electrocardiograms of the proband and his son show prolongation of the QT interval (Fig. 1), but all members of the family were not examined.

Case history and type of attack Nothing special in pre- or postnatal period. Normal somatic development with minor mental disturbance. Pneumonia twice; whooping cough and measles as a child.

He had his first attack at the age of 5 years. There have been only minor variations in the attacks but their frequency has varied. They often start in the early morning when he is asleep and are triggered by fear, excitement, disappointment, or physical exhaustion the previous evening. During the attacks, which are generally brief, he usually adopts an arched position, becomes pale, has irregular respiration, enuresis, and is completely withdrawn. There are no convulsions and no tongue-biting. He is tired and disoriented after attacks.

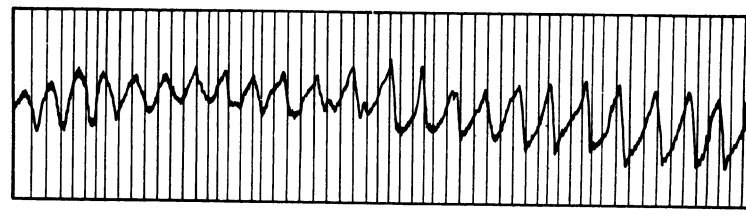
Electrocardiogram The patient has been cared for and examined at the Malmö General Hospital on a number of occasions for these attacks. His abnormal electrocardiogram, with broad T or TU waves, pronounced QT prolongation,[1] and usually sinus bradycardia as well, was noted as early as 1943. The patient was thought to be epileptic at first but an electrocardiogram during an attack while in hospital showed disappearance of the pulse accompanied by ventricular fibrillation, changing to ventricular tachycardia (Fig. 2).

General laboratory tests Repeated serum calcium, serum potassium, and blood sugar determinations were normal. Standard and sleep electrocardiograms, audiograms, electromyographic neurological examinations, cardiac *x*-rays, normal. Intravenous potassium chloride and magnesium sulphate, oral calcium acetate, and exercise tests failed to alter the electrocardiographic pattern. The patient was included in an article on Adams-Stokes disease published by Johansson (1961).

Circadian analysis Since the patient's son developed identical symptoms, with the same daily rhythm, continuous 24-hour electrocardiogram and electroencephalogram recordings were made in October 1969 after all medication had been withdrawn. An arterial catheter was introduced percutaneously into the brachial artery and the blood pressure was measured every hour and blood samples were drawn from the catheter every second hour (Fig. 3). The intention was to confront the symptomatology with the circadian rhythm of different body substances. The patient had no attacks during the recording. The electroencephalogram was normal the whole time. Variations were observed in heart rate and the shape and amplitude of the T wave but no arrhythmias. Serum electrolytes, acid-base status, triglycerides, free fatty acids, plasma cortisol, plasma insulin, and blood sugar, normal. Urinary catecholamines, normal.

Treatment Phenobarbitone, phenopromin, and diphenylhydantoin were used in the treatment but without effect. Atropine may have reduced the frequency of attacks but there is no clear documentation on this point. In February 1967 the patient was started on a course with the adrenergic beta receptor blocking agent, propranolol, in

FIG. 2 *Electrocardiogram during syncopal attack in Case 1 shows ventricular fibrillation–tachycardia.* (See text.)



[1] Ljung's equation, $QT=(R-R)\times 0{\cdot}2+0{\cdot}18\pm 0{\cdot}04$ sec, was used to calculate the QT interval.

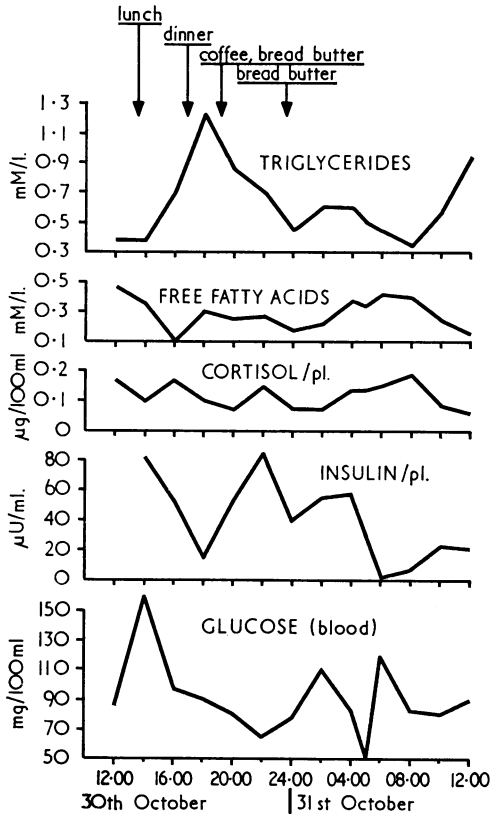


FIG. 3 *Changes in some blood components during 24 hours in Case 1.* (See text.)

relatively small doses (10 mg t.i.d.). Since then the attacks became less frequent and now occur 3 to 4 times a year. Most important of all, the attacks have become milder and shorter. An exercise test before the start of propranolol treatment led to an attack of tachycardia with bundle-branch block. The same exercise undertaken soon after but with the patient on propranolol produced no such changes. No influence on the QT interval has been noted with propranolol and the relation of QT to the complete cardiac cycle has not definitely altered (Fig. 4). Since June 1970 he has been taking 10 mg propranolol each morning and afternoon and 50 mg practolol[1] in the evening and has had no attacks.

Case 2

Boy, 9 years, son of Case 1.

Case history and electrocardiogram Pre- and postnatal history noncontributory. He was admitted to the Children's Department of Malmö General Hospital at the age of 2 months for attacks of bawling. During these attacks, it was noted that he lay with his head bent back and his body arched. Nothing unusual was noted during calm periods, and examination produced no evidence of meningitis or cerebral involvement. An electrocardiogram taken on the day of admission (Fig. 5A) shows broad, slurred ventricular complexes and a value on the upper limit for the QT interval. The ventricular complexes were normal two days later, but the QT interval was clearly prolonged (Fig. 5B).

Somatic development was normal thereafter, but emotional development was bizarre, bordering on psychotic characteristics, and he has been admitted to a department of child psychiatry on two occasions.

Attacks, at varying intervals, appeared after the age of 5, apparently identical to his father's, with the same appearance, and the same circadian rhythm. On three occasions he was studied at Malmö General Hospital because of these attacks, the first time in 1969. He was first thought to suffer from epilepsy. Only two observable attacks were noted during the first period of study, both on the day of admission before any recording devices had been set up. His electrocardiogram was then recorded continuously with a portable cassette tape recorder.[1] Despite the patient's unrest and poor co-operation, two attacks of ventricular tachyarrhythmia were recorded, both at around 4 a.m. without the patient or staff noticing anything (Fig. 6).

At the age of 4 his electrocardiogram was almost identical to his father's, though he had not yet had any attacks. In 1967 an exercise test produced no arrhythmias. Exercise electrocardiograms and phonocardiograms in 1969 disclosed no new developments (Fig. 7).

General laboratory tests Extensive neurological examinations and audiogram, normal. Electroencephalogram (even after sleep deprivation) accompanied by electrocardiogram as well as a continuous electroencephalogram and electrocardiogram recording for 48 hours, disclosed no electroencephalographic abnormalities; the electrocardiographic changes were as before.

Chromosomal analysis, normal. Toluidine blue test, normal. Tests of blood, urine, cerebrospinal fluid, serum urea, creatinine and protein, alkaline phosphatase, free fatty acids, triglycerides, urinary noradrenaline and adrenaline, and serum cortisol were normal. Repeated serum Na, K, Ca, Mg, and P determinations, and blood sugar, normal. The 24-hour blood sugar curve displayed its lowest value of 53 mg/100 ml at 4 a.m.

Treatment After frequent attacks at home, phenobarbitone was started in August 1969 but without effect. The frequency of attacks increased and he was readmitted to hospital in November 1969. No pulse or blood pressure could be recorded during several of the attacks on the first few days of his hospital stay. Propranolol was

[1] Kindly supplied by ICI Ltd, AB Scanmeda, Göteborg, Sweden.

[1] Made by Svenska Radio AB, Stockholm, Sweden. Manufactured by Nukab AB, Fröhusgat 4, Box 2039, S-421 02 Västra Frölunda, Sweden.

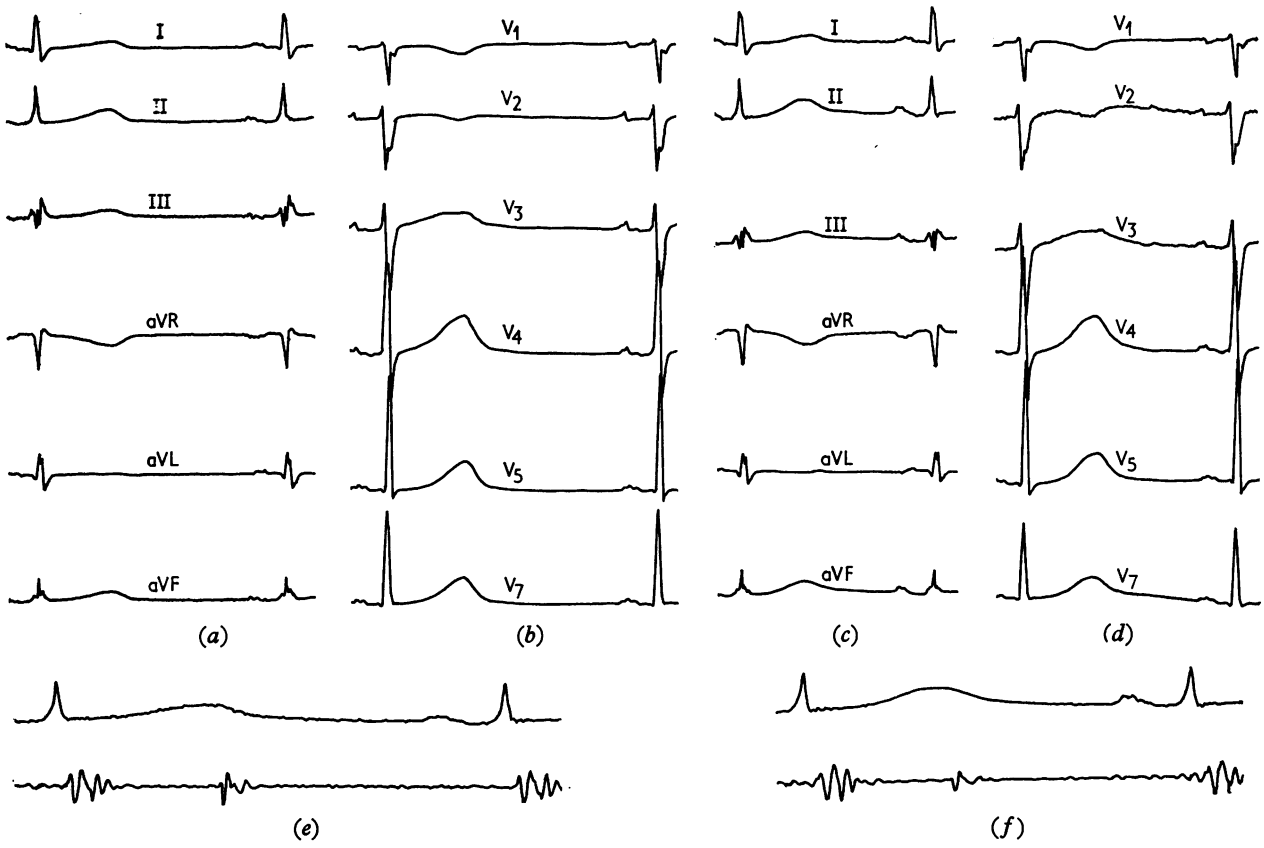
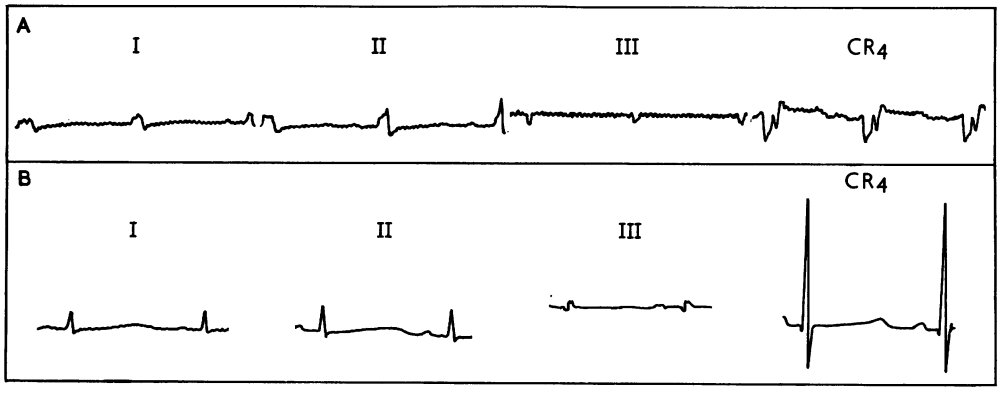


FIG. 4 *Case 1, December 1967. (a), (b), and (e), resting; (c), (d), and (f), immediately after cycling 6 min on 650 kpm/min and 4 min on 900 kpm/min. Paper speed (a), (b), (c), (d), 50 mm/sec; (e) and (f), 100 mm/sec. QT at rest 0·46 sec, during exercise 0·44 sec.*

FIG. 5 *Electrocardiograms in Case 2. (A) At admittance to hospital, 13 January 1962. CR_4 RR 0·42". QT 0·28". Normal upper limit 0·27". (B) After 2 days in hospital. RR 0·54". QT 0·40". Normal upper limit 0·33".*



started and after 3 days his attacks ceased (Fig. 8). In view of his circadian rhythm and normal but relatively low blood sugar at 4 a.m. (as was the case with his father), propranolol was withdrawn, and a slow-acting glucagon drug[1] was given instead. He immediately had an attack, so propranolol had to be reinstated. This was gradually replaced by the adrenergic beta-receptor blocking agent ICI 50 172 (practolol), which is easier to administer – because of the long duration of its action – and is more cardioselective than propranolol. Since Christmas 1969 he has had mild, brief attacks on 3 February, 26 July, and 28 August, plus two ordinary attacks during the second week in November 1970. As with his father, the beta blocking agents had no effect on the QT interval nor QT's relation to the entire cardiac cycle.

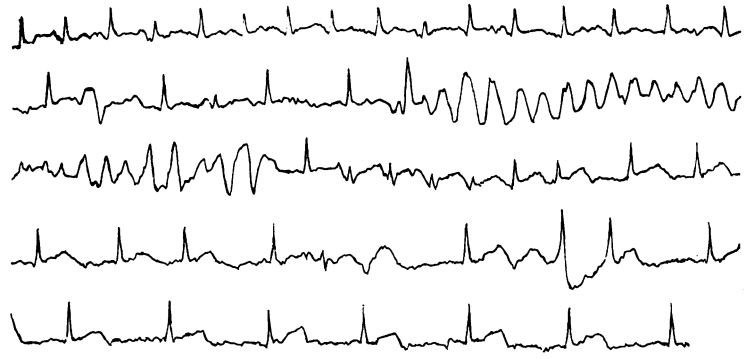


FIG. 6 *Ventricular tachyarrhythmia recorded with portable tape recorder in Case 2.* (See text.)

Discussion

Various theories have been put forward concerning the underlying biochemical, enzymatic or anatomical cause of a prolonged QT interval. Because of the extended period of vulnerability, a long QT interval predisposes the heart to ectopic beats that may trigger ventricular arrhythmias or asystole.

It has been known that certain types of brain damage can produce changes in ST and T segments. Stimuli given experimentally to certain parts of the mesencephalon have induced such changes.

Asymmetrical sympathetic stimulation of the ventricular myocardium leads to conspicuous changes in the T wave and a prolonged QT interval (Yanowitz, Preston, and Abildskov, 1966). The phenothiazine compound, thioridazine, which has been shown experimentally to change the noradrenaline content in cardiac muscle, has also been shown to produce QT prolongation, ventricular arrhythmias, and sudden death (Kelly, Fay, and Laverty, 1963). Certain simple aliphatic aldehydes produce a somewhat selective prolongation of the QT interval, and these aldehydes are closely related to others with a powerful sympathomimetic effect. Hereditary prolongation of the QT interval might therefore be due to abnormal sympathetic stimulation, as postulated by Ward as early as 1964, or to a defect in myocardial noradrenaline metabolism.

The results of examinations and the clinical manifestations in our two patients did not differ from previous case reports of hereditary QT prolongation. Thus, we consistently found severely prolonged QT intervals (though there were large variations between different occasions) and bizarre, varied T or TU waves. Mechanical systole appears normal. In Case 1, an electrocardiogram displaying ventricular fibrillation was recorded during clinical attacks. Both patients had attacks during which no pulse could be palpated. Several attacks of tachycardia were recorded for Case 2 without any clinical symptoms. The lack of symptoms was probably due to the briefness of the attacks. In this context it is worth noting the value of continuous electrocardiogram recordings for detecting attacks. The pronounced daily rhythm of the attacks is remarkable; we have no definite explanation for this. Both patients have a deviant emotional make-up and are neurolabile. There may be some centrally induced, abnormal, sympathetic stimulation of the heart, even though the neurological examinations have been normal.

Atropine has been tried with varying, often unfavourable results in patients with hereditary QT prolongation (Fraser *et al.*, 1964a; Jervell and Lange-Nielsen, 1957; Jervell and Sivertssen, 1967; Lisker and Finkelstein, 1966). Its possible favourable effect in Case 1 is probably attributable to the effect on sinus bradycardia. Sinus bradycardia increases the risk of ventricular arrhythmias, particularly if there is coexistent prolongation of the QT interval.

James (1969) recommends initial therapeutic treatment with phenobarbitone or diphenylhydantoin to protect against centrally triggered paroxysmal sympathetic stimuli. Case 1 received phenobarbitone and diphenylhydantoin and Case 2 phenobarbitone but without effect.

Digitalis, which reduces the QT interval, has been used with varying results on the frequency of attacks (van Bruggen *et al.*, 1969;

[1] Protamine zinc glucagon, supplied by Novo, Malmö, Sweden.

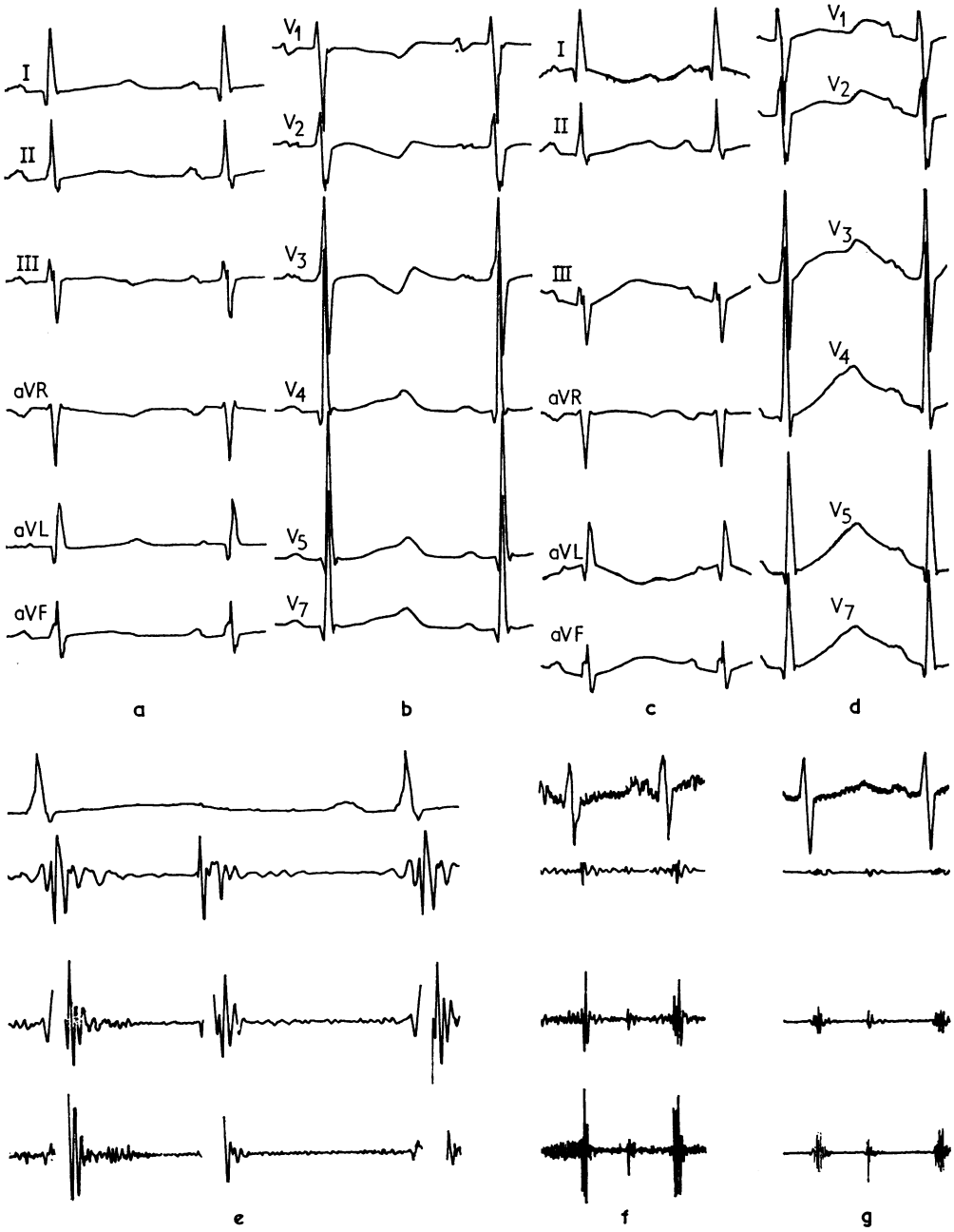


FIG. 7 *Electrocardiogram and phonocardiogram in Case 2 during rest and exercise, April 1969. (a), (b), and (e), resting; (c), (d), and (g) immediately after cycling 10 min on 200 kp m/min and 4 min on 300 kp m/min; (f) cycling 8 min on 200 kp m/min. Paper speed (a), (b), (c), (d) 50 mm/sec; (e), (f), and (g) 100 mm/sec. QT rest at 0·42 sec, during exercise 0·36 sec.*

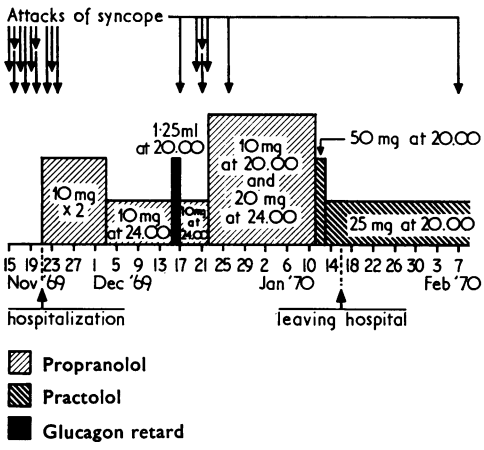


FIG. 8 *Effect of drugs in Case 2.* (See text.)

Dupuis *et al.*, 1969; Fraser *et al.*, 1964a; Gale *et al.*, 1970; Jervell and Lange-Nielsen, 1957; Jervell *et al.*, 1966; Jervell and Sivertssen, 1967; Kallfelz, 1968; Wennevold and Kringelbach, 1971) but involves a risk of triggering ectopic beats.

Quinidine reduces the risk of ectopic beats but extends the QT interval (van Bruggen *et al.*, 1969; Fraser *et al.*, 1964a; Jervell and Lange-Nielsen, 1957).

Pacemaker management was attempted on one patient by Olley and Fowler (1970), who report that the results strongly contraindicate further trials.

Some second thoughts have also been expressed regarding the use of adrenergic beta-receptor blocking agents in such cases. With the slow sinus rhythm often found in these patients, suppression of adrenergic beta-receptors may intensify the bradycardia, predisposing the heart to ventricular arrhythmias. Moreover, if the prolonged QT interval is due to an imbalance in adrenergic action on the cardiac musculature, such drugs may aggravate the imbalance. But the opposite may also be the case: the action of centrally triggered, abnormal sympathetic stimuli on the cardiac musculature may be blocked. Ward (1964) and Gale *et al.* (1970) report good results with these drugs. Our results also appear to indicate a favourable effect of adrenergic beta-receptor blocking agents.

Ten of the 27 cases with a surdocardiac syndrome and 2 of the 31 cases without deafness have died, usually at an early age. Anamnestic data for relatives of these cases suggest that many more may have died from these disorders. Therapy should be initiated without fail. In our view, an adrenergic beta-receptor blocking agent is the drug of choice. The electrocardiogram provides a simple screening method for cases with prolongation of the QT interval; it should not be omitted for children with attacks, whether the disorder is associated with deafness or not. Electrocardiograms should also be made of adults with syncope or other inexplicable attacks.

We should like to express our gratitude to Drs. K. Bülow (Malmö General Hospital), D. Ingvar (Hospital of Lund), and R. Stensman (Hospital of Lund) for their assistance with the continuous electroencephalogram and electrocardiogram recordings. Our sincere thanks, too, to all the others who helped us with the examinations.

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Requests for reprints to Dr. Bengt W. Johansson, Heart Laboratory, Department of Medicine, General Hospital, S-214 01 Malmö, Sweden.