CHRISTMAS DISEASE AND COAL-MINING TRAUMA AND EXPOSURE TO NITROGLYCERINE AS OCCUPATIONAL HAZARDS

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The main features of Christmas disease, a hereditary disorder of blood coagulation, are outlined, and a family of coal-miners who suffer from this disorder is described.

The affected male members of two generations have spent their working lives underground. Three of the eight affected miners were temporarily severely disabled by episodes associated with their bleeding diathesis, and one died in 1894 from haemorrhage following an injury.

A mild degree of Christmas disease caused an increased occupational morbidity in some members of this family, but did not shorten their overall working life-span. Twelve further cases of Christmas disease are briefly described.

One affected man had an episode of cerebral haemorrhage, possibly associated with the physiological effects of contact with nitroglycerine. A review of the literature suggests that nitroglycerine may have a significant aetiological action in the development of cerebral haemorrhage in men with a defective haemostatic mechanism.

Finally, it is suggested that an analogous situation may exist in patients under anticoagulant treatment, who use nitrates or other vasodilator drugs therapeutically.

Christmas disease is one of the hereditary disorders of blood coagulation which is transmitted as a sex-linked recessive trait by females, the clinical manifestations appearing only in the male. It was separated from the other haemophiloid diseases in 1952, simultaneously in England by Biggs, Douglas, Macfarlane, Dacie, Pitney, Merskey, and O'Brien (1952) and in the United States by Aggeler, White, Glendening, Page, Leak, and Bates (1952).

Christmas factor (Factor IX, plasma thromboplastin component) is necessary for thromboplastin generation in the first stage of coagulation and is deficient in this disorder. The clinical and genetic features are indistinguishable from the more common antihæmophilic globulin (AHG or Factor VIII) deficiency (Biggs and Macfarlane, 1957).

Didisheim and Lewis (1958) reviewed all published reports of patients with inherited disorders of coagulation and concluded that the average incidence of Christmas disease was 16% of all patients. Of 106 patients with these disorders who attend the Royal Prince Alfred Hospital, Sydney, New South Wales, 17 (16.0%) have Christmas

disease. Of the remainder, 96% have classical hæmophilia. A summary of 12 cases of Christmas disease who are of employable age, and who are attending R.P.A. Hospital, is given in the Table.

Patients with Christmas disease, like those with classical hæmophilia, show hæmorrhagic manifestations of varying degrees of severity, roughly parallel to the factor deficiency in the blood, which may be measured by the activity of the patient's plasma or serum in artificial clotting systems and expressed as a percentage of the normal level.

Thus a severe case of Christmas disease with a Christmas factor level of 0.1% of normal will have extensive subcutaneous and intramuscular effusions of blood, and, from an early age, recurrent hæmarthroses, all of which may arise from such minimal trauma as to appear "spontaneous". Gastro-intestinal bleeding is common, and hæmorrhage in other sites may, by compression or obstruction of vital structures, cause a variety of syndromes.

Mild cases have a Christmas factor level of 5 to 50% and, generally speaking, only manifest signs of deficient hæmostasis if they are exposed to severe trauma, teeth extraction, or surgical procedures. Hæmarthroses and hæmatomata from

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minimal trauma are rare in this group. There are a few patients with levels of Christmas factor between these two groups, and who are moderately affected clinically. The family to be discussed belongs to the mildly affected group.

Until fairly recently, little has been written about the employment of men suffering from the haemophiloid disorders. This is probably due to previous poor prognosis. Andreassen (1942) gave a life expectancy of about 16 years and authors tended to emphasize the more severely affected patients, who without the benefit of the improved management of the last decade, formed a largely crippled group with poor employment potential (Favre-Gilly, 1957).

However, Quick (1957) stresses that the outlook is far more encouraging now as most haemophiliacs are gainfully employed; some are labourers, exposed to trauma, who work steadily for surprisingly long periods.

Family of Coal-miners with Christmas Disease

There are 13 affected males in five generations of this family (Fig. 1). Three of the affected members in generation III emigrated from Staffordshire in 1923 to the coalfields near Wollongong, N.S.W. In generations II and III all males of employable age worked as coal-miners, but only those with Christmas disease are considered here.

Generation II.—The four affected members in this generation are all dead; their manifestations were described by their relatives. They are said to have had numerous traumatic episodes with persistent haemorrhage or haematomata.

Three lived to the age of 60 or over but the fourth, when aged 45 (in 1894), suffered a compound fracture of the leg in an underground accident and is said to have "bled to death" shortly afterwards.

Generation III

III—1, a boy, 10 years of age, who died from exsanguination due to four days of uncontrollable bleeding

from a lacerated hand (not investigated, the case was detailed by his relatives).

III—2, a man, 72 years of age, with a tendency, noticed at an early age, to bleed excessively after trauma and tooth extraction. For over 30 years he was employed underground, working at the coal-face. Apart from several lacerations and bruises, none of which proved serious enough for admission to hospital, he suffered two major bleeding episodes which required several blood transfusions and treatment in hospital for several weeks. These episodes were an extensive haematoma of the thigh which burst through the skin following a fall of coal onto his leg, and on another occasion, an episode of severe haematuria after being struck in the abdomen by an underground truck. This patient was interviewed personally.

III—3. He was 65 years of age. He remained in Staffordshire and despite frequent haemorrhage into the thigh and calf, he was a skilled soccer player. Although he spent most of his working life at the coal-face he suffered nothing more serious than a few episodes of prolonged bleeding after lacerations, insufficiently severe to require hospital treatment (not interviewed; case described by his brothers).

III—4. He died at the age of 60 after an episode considered by his local doctor to be due to cerebral thrombosis. He was also thought to have suffered from ischaemic heart disease. He spent most of his working life at the coal-face and was in hospital several times for bleeding from lacerations; on two occasions he was given blood transfusion.

This case was described by his attending physician, who was certain that he had a haemorrhagic disorder. The diagnoses of cerebral haemorrhage and ischaemic heart disease were based on clinical observations. No haematological investigation or post-mortem examination was undertaken.

III—5. This patient, 51 years of age, was studied personally in detail. He had his first haemorrhagic manifestation at the age of 4, when he bled for over a week from a lacerated forehead. After numerous traumatic haemorrhages and several troublesome bouts of epistaxis, he had his first blood transfusion at the age of 30 following tooth extraction. In the past 18 months he has had two episodes of gastrointestinal bleeding. In

TABLE
PATIENTS OF EMPLOYABLE AGE WHO ARE ATTENDING ROYAL PRINCE ALFRED HOSPITAL ON ACCOUNT OF CHRISTMAS DISEASE

Case No.	Age (years)	Degree of Severity of Christmas Disease	Occupation	Main Permanent Physical Disability
*1	52	Severe	Housekeeper	Severe arthritis of both knees
2	19	Severe	Watchmaker	Moderate arthritis of both knees
3	17	Severe	Hairdresser	Mild arthritis of both knees
4	19	Moderate	Clerk	Moderate arthritis of right knee
5	17	Moderate	Bank clerk	Moderate arthritis of both knees
6	77	Moderate	Hairdresser (retired)	Severe arthritis of both knees
7	61	Mild	Gas fitter	Nil
8	58	Mild	Sign writer	Nil
9	52	Mild	Lorry driver	Nil
10	51	Mild	Printing press operator	Nil
11	38	Mild	Town clerk	Nil
12	24	Mild	School teacher	Nil

* Case 1 was formerly a pastrycook but had to change his occupation on account of disability.

FIG. 1.—Genealogical tree of the family affected by Christmas disease. NOTE.—Females without offspring may be potential carriers.

1959 coagulation studies demonstrated a haemostatic defect and the thromboplastin generation test (Biggs and Douglas, 1953) showed his defect to be consistent with a mild deficiency of Christmas factor. He started work in the mine at the age of 14 on various underground jobs. For the past 20 years he has been employed as deputy under-manager, and his responsibilities have included the handling and detonation of charges containing nitroglycerine. In his 36 years of employment in a coal-mine he has had four episodes of disability associated with his work. The first two were the result of severe bruising; on one occasion arising from a fall of coal from the roof, and the other resulting from a fall into a coal skip. He was off work for only a few days with each of these episodes. On the third episode he cut his hand severely while inserting a metal sprag into a skip wheel and this led to persistent bleeding over a period of six weeks, with repeated suturing of the wound and several blood transfusions. The last episode occurred in August, 1959. One Monday afternoon he developed his customary headache after handling a moist charge containing nitroglycerine. On returning home he told his wife about the severity of his generalized throbbing headache and went to bed. The following morning he mentioned that he still had his headache, which was most unusual as a short sleep had invariably relieved the numerous headaches he had had previously following contact with nitroglycerine. During work that day he became con-

fused and disorientated, and was put to bed. He then complained of a stiff neck and pain in his back and down the back of his legs, and this continued for three days. Lumbar puncture revealed blood-stained cerebrospinal fluid; the pressure was not recorded. He was then admitted to Royal Prince Alfred Hospital. On admission, he was a man of good physique who was confused and mildly hallucinated. He complained of a severe frontal headache and a stiff neck. He was afebrile. Examination revealed marked neck rigidity, stiffness of the back muscles and a positive Kernig's sign. The other significant neurological findings were diminished power and reflexes in the left arm and a right grasp reflex. There was no external sign of recent head injury. His blood pressure was 160/100 mm.Hg on admission and his Hb 12.6 g./100 ml. Christmas factor level was over 5% of normal. No other abnormalities could be found in any other body system.

A provisional diagnosis of subarachnoid haemorrhage was made and the possibility of a subdural haematoma was also considered. Radiograph of the skull showed no sign of fracture nor of pineal shift. An electroencephalogram showed a grossly abnormal record with right fronto-temporal slow activity considered more suggestive of intracerebral bleeding than of a subdural collection.

Fresh human plasma was given by continuous intravenous infusion, one unit (250 ml.) every four hours for

two days and then one unit every six hours for a further eight days, to raise his level of Christmas factor sufficiently to lessen the chance of further bleeding.

Twenty-four hours after commencing plasma infusions his condition improved and six days later he was perfectly rational and had lost all signs of neurological disturbance. He was discharged from hospital five weeks after admission with no evidence of physical or mental abnormality, but the electroencephalogram still showed a persistent focus in the right fronto-parietal region. Seven months after his initial illness he was still in excellent health and his electroencephalogram was normal.

Generation IV.—The two affected males have been investigated at another hospital and classified as having Christmas disease.

Generation V.—The two affected males were investigated and treated at Royal Prince Alfred Hospital for haemorrhage after trauma. Christmas factor level was over 5% of normal in each case. A summary of 12 further cases of Christmas disease is given in the Table.

It is difficult to classify the disability adequately in these cases. Some are handicapped by recurrent bleeding from peptic ulcer or haemorrhoids, or by haemorrhage into the joints and after teeth extraction or operations. Functionally, haemophilic arthritis of the knees is the sole permanent disability of these people and pain, deformity, or restricted movement in these joints is what troubles them in their occupation. On a functional classification, severe arthritis indicates that the patient is handicapped to the extent of needing assistance (by surgical appliance, crutches, or walking sticks) in carrying out his everyday occupation. By moderate arthritis is meant that the patient can cope with everyday activity without mechanical assistance, but still retains a significant disability, for example in climbing stairs or running. In mild arthritis there is no significant handicap.

All 12 patients are gainfully employed; the retired hairdresser worked until he was nearly 70. Only one patient (Case 1) had to leave his occupation of choice on account of disability and most are in very suitable non-traumatic occupations.

Discussion

Christmas Disease and Coal-mining.—It seems reasonable to assume that the branches of coal-mining in which this family work constitute a source of potential trauma, the effects of which are rendered more disabling or life endangering by the associated haemostatic defect.

Of the 13 males of generations II and III engaged in coal-mining (III—1 died at the age of 10) eight are considered to have Christmas disease and five are normal. There were two occupational deaths in these men; the one, mentioned above, from haemorrhage following a leg injury in 1894, and the other, more recently, when a normal male was

killed in a roof fall. Of the remaining seven with Christmas disease, three appear to have suffered severe temporary disability associated with their occupation and all seven, except the youngest miner (age 51), have reached the seventh decade.

In this family insufficient data were collected to show whether affected males had more occupational morbidity than their normal brothers. However, a mild degree of Christmas disease did not appear to interfere with the long-term employment of those affected. Trauma is the main hazard for affected males, and it is suggested below that nitroglycerine is a possible aetiological factor in the development of cerebral haemorrhage.

Lacerations, particularly of the extremities, are frequent. With modern methods of securing haemostasis by local haemostatic agents, suturing, and factor replacement therapy, where necessary, together with the control of infection, haemorrhage from most wounds should not prove too difficult to control (Sawers, 1958).

Nitroglycerine.—It is possible that the physiological effects of nitroglycerine may have had some aetiological significance in the cerebral haemorrhage of patient III—5. As far as is known, he was the only affected member of his family to use this agent.

The presence of cerebral aneurysm cannot be excluded but this appears unlikely in view of the clinical course, the return of the electroencephalogram to normal in seven months and the high mortality in proven cases. McKissock and Paine (1959) report death in 57% of 355 cases of cerebral aneurysm proven by angiography at operation, or at autopsy. With a superimposed coagulation defect the prognosis in ruptured cerebral aneurysm must be very poor.

Carotid angiography was not undertaken in this patient (III—5), because, even in people with apparently normal haemostasis, a cervical haematoma has caused respiratory obstruction serious enough to warrant tracheotomy (Sugar, Holden, and Powell, 1949).

The patient can recall the events leading to his illness and is certain he sustained no head injury of any nature during the weeks before the onset of symptoms, and this is supported by his wife and workmates and by the negative findings of physical examination.

The patient was not hypertensive, his blood pressure was 130/90 mm. Hg on several occasions during his convalescence, and there was no clinical or electrocardiographic evidence to suggest widespread atherosclerosis affecting the cerebral vessels.

The association of his cerebral haemorrhage with

the severe headache of nitroglycerine therefore seems worthy of further discussion.

The explosive mixture the patient used before his illness contained between 16 : 1 and 14 : 1 parts by weight of nitroglycerine and nitroglycol.

Nitroglycerine (glyceryl trinitrate) is well known as a cause of severe headache and was originally described by Laws (1910) and Evans (1912). The basic action of glyceryl trinitrate is to relax smooth muscle throughout the body, particularly in the finer blood vessels (Goodman and Gilman, 1955a).

Bovet and Gatti (1955) concluded that the cerebral vessels were probably more sensitive to glyceryl trinitrate than the vessels of other regions. Goodman and Gilman (1955b) considered the headache was due to a rise in intracranial pressure caused by dilatation of meningeal and intracerebral vessels. However, Schwartz (1946) concluded that the headache caused by contact with nitroglycerine was closely analogous to that following histamine injection, and Schumacher and Wolff (1941), who studied the histamine headache, found that there was not only a dilatation of the cerebral vessels, but that when the lowered cerebrospinal fluid pressure associated with a reduction in systemic blood pressure was raised, either by vasopressor drugs or by direct introduction of saline into the sub-arachnoid space, the headache was relieved.

On this evidence the two main components of headache caused by these vasodilator drugs appear to be dilatation of cerebral vessels and a fall in cerebrospinal fluid pressure.

It has been shown by Wolff (1955) that in bouts of migraine there may be conspicuous damage to the vascular walls of dilated temporal arteries or their branches. This is manifested by haematomata adjacent to these affected arteries appearing 10 to 60 hours after severe migrainous headaches.

The profound intracranial volume changes caused by the physiological effects of vasodilator drugs might reduce the support for the dilated intracranial vessels sufficiently to damage their walls. When the normal haemostatic mechanism is defective as in Christmas disease the likelihood of significant haemorrhage is greatly increased and a minute vascular leak that would be arrested before it assumed clinical significance in a normal person, could cause serious effects.

In several studies on workers who died suddenly after exposure to nitroglycerine, there was no mention of cerebral haemorrhage found at autopsy, nor was the possibility mentioned. In the absence of any significant pathological findings at autopsy sudden death was ascribed to circulatory collapse due to the effect of nitroglycerine on the cardiovascular system (Symanski, 1952; Forssman,

Masreliez, Johansson, Sundell, Wilander, and Boström, 1958; Maccherini and Camarri, 1959).

Although it cannot be said that nitroglycerine is of any aetiological significance in causing cerebral haemorrhage in normal people, nevertheless, for the reasons outlined above, it may endanger those whose haemostatic mechanism is defective. Workers with any form of coagulation disorder should not have contact with this agent.

The Use of Vasodilator Drugs During Anti-coagulant Therapy.—There is the analogous situation of patients with thrombo-embolic disease, particularly those with ischaemic heart disease, on anticoagulant therapy, who use nitrates or other vasodilators to relieve angina pectoris.

The commonly used anticoagulant drugs are either coumarin or indandione derivatives which cause a deficiency of several coagulation factors, including Christmas factor (Douglas, 1955). Discussing patients on anticoagulant therapy, Peyman (1958) concluded that although the most obvious effect of these drugs was an interference with normal blood coagulation other factors such as capillary damage might be as important, if not more so, in the development of haemorrhage. This observation supports the earlier report of Spaet (1952) who considered a combination of coagulation and vascular defects necessary before a haemorrhagic state was established.

In reports on cerebral haemorrhage during anti-coagulant therapy no information could be found to incriminate vasodilators as an associated cause (see, for example, Russek and Zohman, 1953).

Although there has been no reported relationship between these two groups of drugs in the production of cerebral haemorrhage, their possibly significant association has not apparently been considered.

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