breath, which was cut short as is characteristic with pleural pain. On examination showers of crepitations were heard over the manubrium sterni. No subcutaneous emphysema was found. The temperature did not exceed 99° F. (37.2° C.). An x-ray film of the chest showed a moderately enlarged heart. Three electrocardiograms showed no evidence of myocardial infarction or pericarditis. The pain and pleural signs rapidly disappeared on rest and antibiotic therapy. A similar attack occurred two months later; again there was no evidence of myocardial infarction, and the patient recovered on the same treatment.

In Case 13 the pain closely simulated the pain of myocardial infarction in character and distribution, but crepitations were heard over the sternum and the pain was clearly related to respiration, which suggested the correct diagnosis.

Case 14.—A youth of 19 experienced a sudden severe pain in the chest while heaving some bricks into a truck. He became breathless and distressed. The pain spread to the root of the neck and to both shoulders and arms. The classical signs of air in the mediastinum were found on his admission to hospital, and there was subcutaneous emphysema of the upper part of the chest wall (Hamman, 1939, 1945). The condition cleared up spontaneously in a few days.

Case 15.—A boy aged 14 had been unwell for some days. He developed moderately severe discomfort in his chest, situated retrosternally and without radiation; it was worse on breathing and on effort. On examination a loud pleuro-pericardial friction sound was heard over the front of the chest, and subcutaneous air was noted over the clavicles. He was found to be in diabetic pre-coma. A chest x-ray film showed the typical appearance of mediastinal emphysema with subpleural air separating the mediastinal parietal pleura from the mediastinal structures. There was no pneumothorax.

There is no doubt that in Case 15 the pain was caused by escape of air into the mediastinum, and it is likely that the severe central chest pain which is sometimes felt in spontaneous pneumothorax has a similar origin.

Spontaneous Pneumothorax

Occasionally it may be difficult to distinguish clinically between spontaneous pneumothorax and myocardial infarction. In the former, retrosternal pain may occur with radiation to the neck, jaw, and arms as in coronary occlusion. Possibly this is due in some cases to concomitant mediastinal emphysema, as mentioned previously. It is not only in cases of tension pneumothorax that this distribution of pain occurs, but sometimes in cases where the amount of air in the pleural cavity is small and is difficult to detect clinically. The following case is of this type.

Case 16.—A man of 30 experienced a sudden pain in the left side of his chest anteriorly while preparing his breakfast. It was not particularly severe at the time. He then started cycling to work, when the pain became more severe, was worse on deep respiration, and radiated to the left shoulder and base of the neck, making him breathless. He also noticed weakness, pallor, and coldness of the left arm and hand which lasted about an hour. When seen eleven hours after the onset of the trouble he was not distressed. The left chest wall moved slightly less than the right, and pleuro-pericardial friction sounds and a loud precordial systolic click were heard. A chest x-ray film revealed a small pneumothorax on the left side.

There is little doubt that air had escaped into the mediastinum as well as into the left pleural cavity. The transient pallor and coldness of the left arm was presumably due to arterial spasm, which may have been induced by air in the tissues surrounding the left subclavian artery.

Discussion

No attempt is made to consider the possible mechanisms of referred pain. It is evident that similar pain distributions can be produced by different pathological lesions involving the mediastinal tissues, but it seems that malignant growths in that region give rise more frequently to referral of pain to face and head than do other mediastinal lesions such as myocardial infarction. The whole clinical picture must of course be taken into account in diagnosis, and the value of radiographic and electrocardiographic study is obvious.

Not infrequently, however, it is only after watching the patient over a period of time that the cause of mediastinal pain becomes apparent.

Summary

A wider concept of mediastinal pain is suggested from the study of a number of clinical conditions.

The commoner causes of mediastinal pain are briefly discussed and illustrative cases quoted.

Similarities and differences in pain patterns are noted.

The value of a careful clinical approach is stressed and the use of special investigations indicated.

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A MILDLY AFFECTED FEMALE HAEMOPHILIAC

BY

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Haemophilia, a disease controlled by a sex-linked recessive gene, is naturally very seldom encountered in women. There are a few well-authenticated female haemophilic patients; a family described by Merskey (1951) included three affected females, the daughters of a cousin marriage in a haemophilic family. Israëls, Lempert, and Gilbertson (1951) record another case, that of the daughter from the marriage of a haemophilic patient and a known carrier. In both of these instances later work has shown that the patients had classical haemophilia. In addition, it is occasionally found that female carriers of haemophilia have some unusual tendency to bleed (Fantl and Margolis, 1955); it is presumed that the abnormal gene is only partially recessive in these patients.

The girl whose case is described here is unusual because when first encountered she had no knowledge of any other affected member of the family. The case is worth recording because it illustrates features in the management of haemophilic bleeding.

Case Record

On July 7, 1956, a 19-years-old girl, who was dangerously ill with uncontrollable post-operative bleeding, was flown into the centre of Oxford by helicopter from Bournemouth and admitted to the Radcliffe Infirmary under the care of Professor L. J. Witts.

When the patient was 3 years old her mother and father separated and she was subsequently brought up by her father. On questioning she said that she knew of no other instances of abnormal bleeding in the family. Her childhood had been uneventful, and the only indications of an abnormal bleeding tendency were rather heavy periods and three weeks' bleeding from a tooth socket following extraction of a single tooth in her early teens. The bleeding

was not severe enough to prevent attendance at school. Another extraction two years later was uneventful.

In August, 1955, she was delivered of a healthy full-term male child and following delivery there was continuous bleeding from a vaginal laceration, despite repeated suturing and packing of the vagina. After two weeks the right internal iliac artery was ligated, but bleeding continued for another three days. She was in hospital three months, and was transfused with 37 pints (21 litres) of blood. At that time laboratory tests gave the following results. Bleeding-time: 2½ minutes; clotting-time, 11 minutes (Lee and White); prothrombin time, 14 seconds; prothrombin index, 100%; platelets, 195,000 per c.mm. All these results were normal and the cause of bleeding remained obscure.

She was well until five weeks before her transfer to the Radcliffe Infirmary, when she was admitted to a Bourne-mouth hospital with a heavy vaginal haemorrhage and epistaxis. A diagnosis of incomplete abortion was made. On dilatation and curettage quantities of placental tissue were removed. Vaginal bleeding persisted, and four weeks later a further curettage was done, but this failed to improve her condition and blood was transfused almost continuously. Ten days before she came into our care she underwent an emergency abdominal hysterectomy and right salpingo-oophorectomy, following which blood loss per vaginam continued and abdominal bleeding started. The day before her transfer she had a brisk vaginal haemorrhage. The vagina was packed and she was given 180 ml. of fibrinogen solution, followed by 2 pints (1,140 ml.) of blood. It was then found that there was a large tender mass in the abdomen arising out of the pelvis.

When she arrived in Oxford she looked much fitter than we had expected, and her chief complaint was of colicky pains in the lower abdomen. Physical examination revealed a vertical midline incision in the lower abdomen 11 cm. long, already partly healed. The clips and sutures were still *in situ*. The lower abdomen was tense and tender, and there appeared to be both a thickening of the layers of the abdominal wall under the scar and also a large mass rising out of the pelvis. It was thought that both abnormalities were due to haematomata. A slight loss from the vagina of dark offensive-smelling blood was noted. The patient was incontinent of small quantities of rather turbid urine. Passage of a catheter did not reveal any residual urine.

Investigation of the Bleeding Tendency

Routine tests on admission gave the following results: haemoglobin, 84% (12.4 g. per 100 ml.); W.B.C. 6,700 per c.mm.; E.S.R., 32 mm. in 1 hour (Westergren); platelet count, 606,000 per c.mm.; bleeding-time, normal; tourniquet test, negative; clotting-time (Lee and White), 6 minutes (normal); prothrombin consumption index, 16–31% (abnormal); one-stage prothrombin time, normal; two-stage prothrombin, 90% (normal).

The only definitely abnormal result was the raised prothrombin consumption index. Further investigation revealed an abnormal thromboplastin generation test, inability of the patient's plasma to correct the clotting defect in known haemophilic blood, and a level of antihemophilic globulin (A.H.G.) of 18–25% of normal.

These results showed without doubt that the patient had a mild degree of classical haemophilia, a conclusion so unlikely in the absence of any family history that the patient's father was asked to attend the hospital as soon as possible (the whereabouts of her mother was not known).

FIG. 1.—Family history of the patient, who is III 17. Her brother's blood was tested. The other clinically affected members (II 12 and III 1 and 4) are all dead.

From him and, later, from the patient's mother, who was traced and interviewed, the true family record was obtained (Fig. 1). It was then clear that the family included four severely affected male haemophiliacs, including the patient's own brother, and that the patient's mother was a carrier of haemophilia.

The patient's mother, father, brother, and baby son were tested and the following results obtained:

	Patient's Mother	Patient's Father	Patient's Brother	Patient's Son
Clotting-time . .	8½ min.	5 min.	More than 40 min.	2½ min. (capillary blood).
Level of A.H.G. 71%		Normal	0	17%

The brother's blood gave the results of a severely affected haemophiliac and his history of repeated bleeding episodes confirmed the diagnosis. No abnormality was detected in blood samples from the mother and father. The father had experienced no abnormal bleeding. The patient's mother gave a history of menorrhagia and bleeding for one week following the removal of seven teeth, and later for one to two weeks following the removal of 21 teeth. Delivery of her children was uneventful, and an abdominal operation was not followed by excessive bleeding. Clearly the

mother's bleeding tendency was less severe than that of her daughter. The low A.H.G. level of the patient's son is interesting. So far, at 14 months, he is entirely normal, but bleeding in patients with this level of A.H.G. is seldom occasioned by anything but quite severe injury.

It is difficult to suppose that the patient is a carrier of an incompletely recessive haemophilic gene. Were this the explanation her mother might be expected to be **equally** severely affected. Moreover, the patient's son should be either a normal male or a severely affected haemophiliac. The level of 17% of A.H.G. recorded in his blood is similar to that of his mother. The only obvious explanation is that the patient is a carrier of severe haemophilia and that the remaining gene has been modified to produce mild haemophilia. The son has fortunately inherited the gene for mild haemophilia (Fig. 2).

FIG. 2.—Diagram to illustrate the possible hypothesis to explain the clinical and laboratory findings in the patient and her relatives. The patient's mother is a carrier of severe haemophilia. The father is normal. It is assumed that a mutation for mild haemophilia has occurred in the sperm carrying the father's X chromosome to the patient. The patient's son is assumed to have inherited the X chromosome which carries mild haemophilia.

Progress While in Hospital

On July 11 a large clot appeared at the vulva and oozing continued. During this day her pulse rate rose and her blood pressure fell gradually, and she continued a low-grade pyrexia of 99–100° F. (37.2–37.8° C.).

On July 12 a limited vaginal examination was carried out by Professor Moir, who found a firm mass in front of and above the vagina, and a large clot coming through the wound in the vault. There seemed to be an extensive haematoma, partly in the abdominal wound but probably also extending round the bladder and into the lower pelvic peritoneum. It was decided to open the abdominal incision and attempt to evacuate the underlying clot, following a fresh plasma transfusion.

Next day she was given 1 litre of fresh plasma in 70 minutes. This raised her A.H.G. level to 50% and the prothrombin consumption index fell to 13%. At the end of the transfusion and under general sedation and local

analgesia a 3-cm. incision was made in the lower part of the scar and 3–4 oz. (85–114 ml.) of clot was removed; but this made little difference to the contour of the abdomen, and it was felt that most of the bleeding was interstitial and generalized, as it so often is in haemophilia. A fuller vaginal examination was done, a large offensive-smelling clot was removed, and a swab was taken for bacterial culture. The impression of a large haematoma in the pelvis was confirmed.

On July 14, following the examination of the previous day, there was little vaginal bleeding, but her haemoglobin level had fallen from 13.3 g. per 100 ml. on July 10 to 7.1 g. per 100 ml. It should be mentioned here that it was never possible to measure the rate of bleeding either from the vaginal loss, which was mainly of days-old clot, or by palpation of the lower abdomen, in which the size of the haematoma fluctuated from day to day. The pulse and the patient's own well-being proved the most useful guides to therapy.

She was given 1 litre of fresh plasma and 1 litre of fresh blood, and from this time on frequent similar transfusions were given. Large clots were passed with almost unchanging frequency (about four clots a day) per vaginam, and the haemoglobin level was maintained at an average of 10 g. per 100 ml., falling as low as 5.9 g. on July 20, and rising to 13.5 g. on August 6. The presence of vaginal clots caused her great discomfort and removal always gave relief. A culture of *E. coli* was obtained from clot and urine. The organism was insensitive to penicillin V, which she had been taking, but sensitive to chlortetracycline, which was started on July 15. She became afebrile, but her temperature rose again on July 26, when the chlortetracycline was stopped. From then on sulphadimidine and penicillin V were given and she remained afebrile up to the time of discharge. Her general condition improved with the control of infection, and from July 15 there was a steady reduction in the apparent size of the pelvic mass, as judged by abdominal palpation, and micturition returned to normal in spite of continued bleeding.

During her treatment in Oxford she was given 13½ litres of fresh plasma, 9 litres of fresh blood, and 5 litres of stored blood. On average the A.H.G. level was raised to 45% by the transfusion of 1 litre of fresh plasma.

On July 29 she had a minor rigor after plasma transfusion, and this recurred on July 30 after plasma. There were fortunately no further similar reactions. On July 31 she woke up to find the eyelashes of all four lids had fallen out on to the sheet in the night. There were no signs of local inflammatory change, and we have not been able to explain this. Fortunately, new growth soon started again.

On August 6 the amount of clot passed seemed to be less and it again had a foul smell. We were inclined to take the pessimistic view at this stage, and assumed that she must be forming an infected pelvic haemorrhagic "cyst." To our surprise and satisfaction she improved from then on. Transfusions and clots became less frequent and smaller, and her haemoglobin slowly rose. The abdominal wound was completely healed.

On August 11, six weeks and three days after operation, the bleeding finally stopped, and from then she improved rapidly and finally left hospital in good health one month later, her only complaint being of some urgency of micturition. Her abdomen was quite normal on palpation.

Discussion

In the absence of any clear indication of haemostatic defect, excessive bleeding in a female is particularly disconcerting. There is the natural tendency to attempt to control the bleeding by methods known to be effective in haemostatically normal people. In this patient the defect was haematologically so slight that it was unlikely to be detected in any but a specialist laboratory, and the patient's ignorance about her own family prevented any specific search for haemophilia.

Had the diagnosis been clear from the onset the general management of the case would undoubtedly have been different. Haemophilic bleeding cannot be controlled without restoring a normal clotting mechanism. Had the true problem been appreciated, the first curettage would have been preceded by a big transfusion of fresh plasma. Thereafter the local bleeding site would have been left alone to heal and bleeding treated by transfusion of fresh plasma and whole blood. Any extension of the bleeding area by operation can only increase bleeding in a haemostatically abnormal patient.

It may be wondered why the patient's bleeding was so persistent and rapid even after her haemostatic mechanism was virtually controlled by transfusion. When first seen at the Radcliffe Infirmary she was bleeding from an inaccessible secondarily infected site. In such a wound the vessels are not normally contractile and, unless local pressure can occlude the blood flow temporarily, normal coagulation cannot arrest the bleeding. In such adverse circumstances it is necessary to have great patience and to recollect that haemophilic bleeding is usually finally arrested by healing.

Summary

A female patient, apparently suffering from mild haemophilia, was admitted to hospital with severe post-operative bleeding. Her progress and treatment in hospital are described. A study of her near relatives was made.

We thank Professor L. J. Witts for permission to publish the case; Mr. J. W. Nankivell for referring the case; and Drs. O. Gunnery, E. R. Jones, and N. M. Parkes for help in obtaining samples of blood from relatives. We also thank the Oxford Regional Blood Transfusion Service, whose very helpful co-operation was largely responsible for the patient's recovery. Miss Ruth Anderson carried out the laboratory tests on which the diagnosis was based. Dr. R. G. Macfarlane and Professor L. J. Witts kindly read the manuscript.

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VENO-OCCLUSIVE DISEASE OF LIVER IN AFRICAN CHILDREN

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All the publications on veno-occlusive disease of the liver have originated from Jamaica, where it is reported as occurring predominantly in children (Jelliffe *et al.*, 1954a, 1954b; Bras *et al.*, 1954) and more rarely in adults (Stuart and Bras, 1955). The authors who observed this condition in Jamaica had never seen it while working in equatorial Africa, in Indonesia, or in the temperate zones (Jelliffe *et al.*, 1954b). However, cases of this nature are said to have occurred in Egypt (F.A.O.-W.H.O.-Macy Foundation, 1955, p. 76).

In 1953 Hill *et al.* described a hepatic syndrome in Jamaican children clinically identical with veno-occlusive disease of the liver. They termed this syndrome serous hepatosis on the basis of certain histological observations. However, on reviewing their cases subsequently they found that these showed the histological picture of veno-occlusive disease of the liver (Addendum to Jelliffe *et al.*, 1954b; Bras and Hill, 1956).

Veno-occlusive disease of the liver occurs most commonly in children between the ages of 1½ and 3 years,