lants who were maintained with prothrombin times of less than 60% of normal. Brambel[9] found that protection appears to be offered when anticoagulants are used prophylactically if the prothrombin level is maintained at 40% to 50% of normal. Cosgriff[10] kept 28 patients with recurring embolism on prophylactic anticoagulant therapy with a range of prothrombin times of 30% to 15% of normal. With this programme he found that 103 emboli had occurred during 275 patient-months prior to treatment, compared with 13 emboli during 625 patient-months under therapy. Furthermore approximately three-quarters of the 17 patients in whom long-term use of anticoagulants had been discontinued suffered another embolism.

On the basis of the above figures our patient has been maintained continuously within a successful "therapeutic" range. In only four instances was the prothrombin level greater than a value corresponding to 30% of normal prothrombin activity, and even these four determinations represented values below the range of 40% to 60% of normal considered effective by the above-mentioned authors in the prophylaxis of thromboembolism. The obvious principle that therapeutic success with lessened danger of bleeding could be obtained by aiming at a relatively lesser prothrombin reduction was, therefore, adhered to in the case under consideration. The one bleeding episode which occurred with a markedly prolonged prothrombin time did so without any apparent precipitating cause. Fortunately with the availability of fat soluble vitamin K preparations such situations can be fairly quickly reversed.

It should also be noted that long-range studies (two days to 56 months) by Meitus *et al.*[11] in 45 patients have revealed no evidence of appreciable hepatic parenchymal damage in patients on dicoumarol who had not previously suffered from liver disease.

SUMMARY

Another case is added to the growing list of patients with intracardiac thrombosis and recurring embolization who have been kept on continuous anticoagulant therapy with a significant reduction in further embolic episodes. In this instance, a 36 year old woman has been successfully maintained on dicoumarol for 11 months with no further recurrence of emboli. One bleeding episode was successfully treated with vitamin K_1.

REFERENCES

1. WEISS, S. AND DAVIS, D.: *Am. Heart J.*, **9**: 45, 1933.
2. DALEY, R., MATTINGLY, T. W., HOLT, C. L., BLAND, E. F. AND WHITE, P. D.: *Am. Heart J.*, **42**: 566, 1951.
3. SPRAGUE, H. B. I. AND JACOBSON, R. P.: *M. Clin. North America*, **32**: 1309, 1948.
4. COSGRIFF, S. W.: *J. A. M. A.*, **143**: 870, 1950.
5. FOLEY, W. T. AND WRIGHT, I. S.: *Am. J. M. Sc.*, **217**: 136, 1949.
6. HINES, E. A. AND BARKER, N. W.: *M. Clin. North America*, **33**: 335, 1949.
7. QUICK, A. J.: *Am. J. Clin. Path.*, **10**: 222, 1940.
8. GRIFFITH, G. C., STRAGNELL, R., LEVINSON, D. C., MOORE, F. J. AND WARE, A. G.: *Ann. Int. Med.*, **37**: 867, 1952.
9. BRAMBEL, C. E., HUNTER, R. E. AND FITZPATRICK, V. DE P.: *Bull. School Med. Univ. Maryland*, **35**: 91, 1950.
10. COSGRIFF, S. W.: *Ann. Int. Med.*, **38**: 278, 1953.
11. MEITUS, M. L. AND WASSERMAN, P.: *Arch. Int. Med.*, **91**: 464, 1953.

ADDENDUM:—A total of 18 months has now elapsed since the onset of treatment. The patient continues at a favourable prothrombin level without further embolization or bleeding.

FANCONI'S ANÆMIA (APLASTIC ANÆMIA WITH CONGENITAL ABNORMALITIES)*

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TWENTY-THREE CASES of aplastic anæmia with congenital defects—described first by Fanconi—have been published to date. We have recently followed up a further patient who had two siblings affected by this syndrome, which, so far as we know, has hitherto not been described in Canadian medical literature.

The parents of the child (both of Ukrainian origin but not consanguineous) came to Canada 30 years ago. The oldest brother, born in 1927, is alive and well. The second brother, born in 1928, had small thumbs on both hands. He died three days after birth. The next three siblings—a brother 23 years, sister 19 years and brother 15 years—are apparently normal. The next child, a girl, was born in 1942. She had no thumbs; her forearms were shorter than normal, and both hands were flexed radially. Radiographs taken at the age of four showed absence of both radial bones and delayed ossification centres of the right carpal region. This girl was noted to have darker skin than the other siblings. At the age of nine, she developed measles with a typical rash, and five days from the onset of the measles she was admitted to a country hospital because of nasal and rectal hæmorrhage, fever and pneumonia. Her hæmoglobin value on admission to hospital at that time was 22%. Blood transfusions and antibiotic therapy did not achieve improvement, and the patient was discharged home, when she died in June of 1951. (These data were kindly furnished by Dr. M. E. Chonko, Two Hills, Alberta.)

*Not to be confused with other "renal" Fanconi's syndrome.

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The patient here reported was the youngest child in the family, and was nine years of age when seen by us. Pregnancy and delivery in her case had been normal, and the child is alleged to have developed at a normal rate and to have been making satisfactory progress at school. During the past two years, she had frequent nose bleeds, bruised easily, and complained of weakness and nervousness. Six months prior to admission to this hospital she had a severe epistaxis, since which she has been unable to attend school. She was sent to this hospital on April 24, 1953 for investigation.

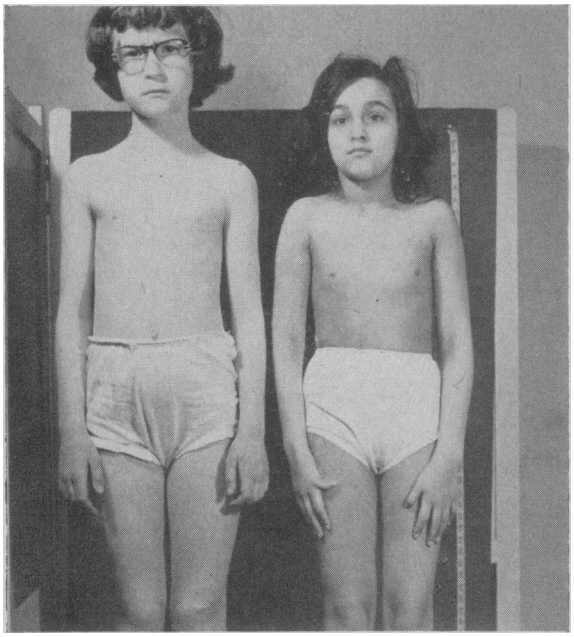

Fig. 1.—Patient (right) and normal girl of her age.

On examination, her stature was found to be smaller than average for her age (Fig. 1). Her weight was 50 pounds. The skin was uniformly dark with olive tint. No petechiæ or bruises were present. The head was smaller than normal, and microphthalmia was noted. The occipito-frontal diameter on lateral radiographs of skull was 17 cm., as compared with 20 cm. and 21 cm. in two normal girls of the same age. The right thumb was much smaller than normal and attached loosely only by the skin. It could be moved passively in all directions but no active movements were possible. The left thumb was smaller than normal, and in form more similar to the other fingers than to a thumb (Fig. 2). No other bony deformities were detected. The ears did not show visible abnormalities, but hearing was grossly impaired on both sides. The girl did not hear when spoken to in a low voice, but stated that she heard the tuning fork from a distance too great to be possible. The fundi showed normal discs without physiological cupping. In the right fundus, two large hæmorrhages radiating from the disc towards the periphery were seen. The chest was clear. A soft, grade 1 systolic murmur was heard over the apex and in the second intercostal space, both to the left and right of the sternum. The liver was palpable just below the costal margin. The spleen was not palpable.

Reflexes.—Knees—markedly hyperactive; ankles, biceps, triceps, and supinator—slightly hyperactive. No true clonus. No other neurological abnormalities were detected. The child's intelligence appeared normal but rapport was difficult to establish because of her deafness. Bone marrow was aspirated from the iliac crest, and smears showed a very acellular marrow giving a differential of:

	%
Neutrophil polymorphs	7
Neutrophil stab cells	5
Neutrophil metamyelocytes	1
Lymphocytes	50
Acytoplasmic nuclei	24
Eosinophil polymorphs	1
Reticulum cells	3
Unidentified cells	1
Intermediate normoblasts	1
Late normoblasts	7

No megakaryocytes or megaloblasts were seen in the smears of marrow, in which numerous crystalline and amorphous clear bodies were seen and later shown to be fatty acid crystals. Other laboratory findings are given in the table.

Skin biopsy from the abdominal wall showed a marked increase in the amount of pigment in the basal and lower prickle cell layers together with free pigment in the upper corium and also in large melanophores in the same area. Special staining for iron gave negative results, and it was presumed that the brownish pigment was of melanin nature.

Chest radiographs were normal. Those of the right hand showed under-development of the bones of the right thumb and first metacarpal bone with a thin radius, and six carpal ossification centres (normal for her age eight). Radiographs of the left hand showed a short last phalanx of thumb, and seven carpal ossification centres (Fig. 3). The feet were moderately decalcified but otherwise normal. The radiograph of the skull was normal, with a normal sella turcica. Intravenous pyelography showed normal kidneys.

During her nine-day stay in hospital, the patient ran a temperature of from 98 to 100° F. She received seven blood transfusions, each of 250 ml., without any reaction. After five transfusions, her hæmoglobin value rose to 8.6 gm. (59%) and her erythrocyte count to 2.9 million, while her platelet count appeared to rise to 90,000. The patient was discharged on May 3, 1953, and the parents were advised to take her to her country hospital for

TABLE OF LABORATORY FINDINGS

Peripheral blood	Red cell count 1.2 million: Hb 3.5 gm. (24%); M.C.H. 29.1.
White cells	4,500 per c.mm.; polymorph 30%; lymphocytes 65%; monocytes 4%; eosinophils 1%; normoblasts 1%; reticulocytes 0.5%; platelets 60,000 per c.mm. Anisocytosis—slight. Schistocytes present; blood group B, Rh-negative.
Coagulation	clotting 9½ mins. (Lee-White); prothrombin time 16 sec. (80%).
Coombs test	Negative.
Red cell fragility	Hæmolysis began in 0.45% and was complete in 0.3% saline.
Capillary fragility	No petechiæ (5 min. at 80 mm. Hg.).
Serum bilirubin	Total 0.25 mg. %.
Serum protein	Total 6.9. gm.; albumin 3.4 gm.; globulin 3.5 gm. %.
Urinalysis	Negative. No porphyrins or porphobilinogen present.
Blood sugar	Fasting 100 mg. %; 3 hr. p.c. 125 mgm. %.
Thorn test	Eosinophils at 8 a.m. 69 per c.mm.; at 12 noon 103 per c.mm. Uric acid/creatinine ratio: 1st specimen 82.1/136.3 = 0.6; 2nd specimen 44.3/36.3 = 1.22.
Kepler-Power test	Night specimen 100 ml.; 8.30 a.m. 58 ml.; 9.30 a.m. 42 ml.; 10.30 a.m. 124 ml.; 11.30 a.m. 23 ml.; 12 noon 20 ml.
Serum sodium	161 meq/l. (uranyl zinc acetate method—not checked).
Serum chloride	106.1 meq/l.

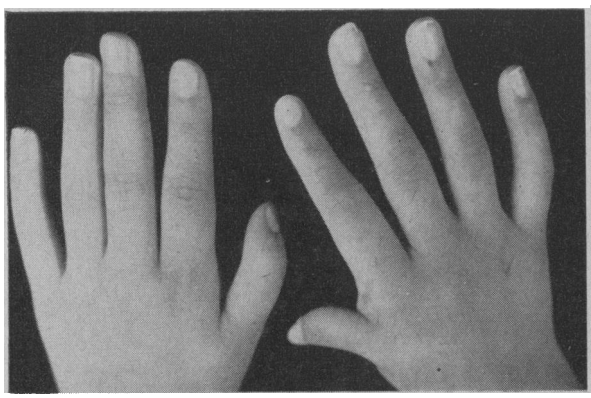

Fig. 2

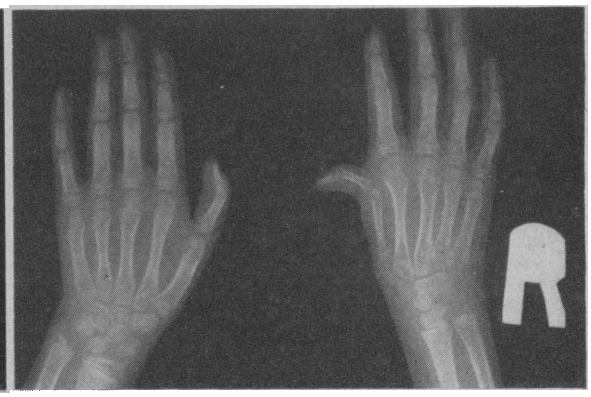

Fig. 3

Fig. 2.—Right and left hand of the patient. Fig. 3.—X-ray of both hands.

more blood transfusions. One week after returning home, nose bleeds again set in and nasal packing was required. Her hæmoglobin value just after the onset of the nasal hæmorrhage was 30%. Several blood transfusions were required as her epistaxis increased. She ran a slight fever despite antibiotic therapy. On May 20, the patient died at home. No autopsy was performed.

DISCUSSION

The diagnosis was certain in our case. Aplastic anæmia with leukopenia, thrombocytopenia, congenital defects of thumbs, microcephaly, deafness, microphthalmia, dark colour of skin, exaggerated tendon reflexes, familial incidence – all these fit perfectly into the condition first described by Fanconi.[1] Since Fanconi's publication, only a few cases of familial incidence of this syndrome have been described (Weil,[2] Hjorth,[3] Dacie and Gilpin,[4] Rohr,[5] Levy,[6] Kunz[7]). Several sporadically occurring cases have been reported, by Uehlinger,[8] Van Leeuwen,[9] Weil,[2] Zellweger and Zollinger,[10] Estren, Suess and Dameshek,[11] Diamond,[12] Beautyman,[13] Baumann,[14] Young *et al.*,[15] and Silver, Blair and Kempe.[16] An exhaustive review of the literature was recently published by Kunz.[7]

Elevation of the reticulocyte count and abnormal fragility of the red blood cells were present in six reported cases, and elevation of serum bilirubin level was noted in five cases, but all these findings were absent in our patient. Macrocytosis and the presence of schistocytes were noted in our case, but anisocytosis was slight.

Kunz suggested impaired adrenal function as the cause of some of the manifestations of this syndrome. His view was based on the findings by Gasser and Hollander (Kunz[7]) of a low kestosteroid excretion in the second case of Rohr, and a positive Kepler test and suggestive changes in serum electrolytes in the same case. In our case, however, Kepler and Thorn tests were normal and the serum sodium value was high. We agree with Kunz as regards the striking resemblance of all these patients to each other in the published photographs. Our patient resembles very closely the photograph given by Beautyman.

Out of 26 patients reported to date, (including the three here described), only one recovered, this patient being without congenital defects (Dacie and Gilpin[4]), and two are alive (Rohr and Beautyman, cited by Kunz). As far as treatment is concerned, only blood transfusions and antibiotics remain of certain value in prolonging life. Splenectomy seemed helpful in the case of Dacie and Gilpin, and improved initially the patient of Estren *et al.*, who, however, died subsequently (Kunz). In other cases no change in the course of the disease was noted. Gasser and Hollander used cortisone unsuccessfully in two cases (Kunz).

It seems to us that the syndrome above described is not as rare as might be judged from the small number of reported cases. Probably, in many cases the diagnosis is missed. It is characteristic that several cases were published from Zürich,[1, 5, 8, 10] and a number of the remainder from big centres in the United States. The full description of the syndrome has never appeared in general journals in the English language, and may well be unknown to many practitioners and orthopædic surgeons who may have occasion to see such cases. Probably also, many more patients with multiple congenital defects do not live long enough for the development of the characteristic anæmia, which usually appears around the age of seven years. In such patients, proper diagnosis must remain presumptive. As an example of such a case, we may mention a three day old baby recently brought to our attention

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by Dr. M. Milner. This child had a marked radial deviation of the left hand due to absence of the radius, the left thumb being also absent. The right thumb was like a second finger and was attached only by skin, while the radius on the right side was hypoplastic and the hand radially flexed on that side. In addition, this baby showed multiple anomalies of the vertebræ, mostly in the form of hemivertebræ. The hæmatological picture was normal: erythrocyte count 6.4 m., Hb 18.4 gm. (127%), white cell count 10,600, polymorphs 40%, lymphocytes 46%, monocytes 10%, eosinophils 4%, platelets 500,000.

Fanconi's syndrome may have an importance beyond its rarity in that it may help to explain the etiology of other aplastic anæmias without toxic causes on the basis of a congenital defect of bone marrow. If this syndrome may occur with one or more congenital defects, it is conceivable also that in some cases the only defect may be that affecting the marrow. Eight such cases in two families have been described by Estren and Dameshek,[17] and one whose sibling had anæmia and congenital defects by Dacie and Gilpin.[4]

SUMMARY

Three cases of aplastic anæmia with congenital defects (Fanconi's anæmia) of familial occurrence are presented. The possible connection of this syndrome with idiopathic aplastic anæmias is briefly discussed.

Our thanks are due to Mr. Z. A. Zielinski, Photographer, Royal Alexandra Hospital, Edmonton, for the photographs.

REFERENCES

1. FANCONI, G.: *Jahrb. f Kinderh.*, 117: 257, 1927.
2. WEIL, P. E.: *Sang*, 12: 389, 1938.
3. HJORTH, P.: *Nord. med.*, 7: 1313, 1940.
4. DACIE, J. V. AND GILPIN, A.: *Arch. Dis. Childhood*, 19: 155, 1944.
5. ROHR, K.: *Blood*, 4: 130, 1949.
6. LEVY, W.: *J. Pediat.*, 40: 24, 1952.
7. KUNZ, H. W.: *Pediatrics*, 10: 286, 1952.
8. UEHLINGER, E.: *Klin. Wchnschr.*, 8: 1501, 1929.
9. VAN LEEUWEN, H. C.: *Folia Hæmat.*, 49: 434, 1935.
10. ZELLWEGER, H. AND ZOLLINGER, H. U.: *Helvet. pædiat. acta*, 1: 382, 1946.
11. ESTREN, S., SUESS, J. F. AND DAMESHEK, W.: *Blood*, 2: 85, 1947.
12. DIAMOND, L.: In Mitchell-Nelson Textbook of Pædiatrics, 5th ed., W. B. Saunders Company, Philadelphia and London, p. 1128, 1950.
13. BEAUTYMAN, W.: *Arch. Dis. Childhood*, 26: 258, 1951.
14. BAUMANN, T.: *Ann. pædiat.*, 177: 65, 1951.
15. YOUNG, L. E., PLATZER, R. F., ERVIN, D. M. AND IZZO, M. J.: *Blood*, 6: 1099, 1951.
16. SILVER, H. K., BLAIR, W. C. AND KEMPE, C. H.: *Am. J. Dis. Child.*, 83: 14, 1952.
17. ESTREN, S. AND DAMESHEK, W.: *Am. J. Dis. Child.*, 73: 671, 1947.

MALIGNANT THYMOMA*

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MALIGNANT THYMOMA is fortunately a fairly rare condition. According to Boyd[1] "Malignant thymoma resembles in structure a lymphosarcoma, but careful examination will reveal a difference. The cells are larger than those of the typical lymphosarcoma, large pale cells recalling those of Hodgkin's disease may be seen, and occasionally giant cells are present. Although it is commonly thought that the cells are derived from the lymphoid cells of the gland, Ewing and others consider that they originate from the reticulum cells." These tumours "compress and invade the surrounding structures, and may extend downward as far as the diaphragm. The bronchial, cervical and axillary lymph nodes may become involved. Thymoma forms a variety of mediastinal tumour. Metastasis to distant organs sometimes occurs."

Both Bell[2] and Moore[3] mention thymoma but do not add a great deal to the general picture. Rider and McDonald[4] and also H. Levine[5] mention malignant thymoma in reports published in 1950.

I wish to report a case which I saw recently.

CASE HISTORY

E.G., a girl of 13, was referred to me on March 26, 1953, with a history of having been treated for enlarged glands in the neck five days previously. She was given large doses of penicillin and sulphonamides without relief and the glands continued to enlarge.

On the morning of March 26 the mother informed the family doctor that her child had had several very severe episodes of choking, difficulty in breathing and cyanosis. The mother took the child to the local hospital where she was given oxygen periodically. The family doctor saw her in one of these attacks and felt quite concerned. He thought that he might be dealing with a Ludwig's angina with a possible acute œdema of the glottis.

I saw her about 8 p.m. on March 26. She appeared to be a very happy teen-ager without any distress. There was tremendous swelling of the neck reaching from the submental area to the supraclavicular notch. This mass seemed to be fairly soft but there appeared to be hard lymph nodes at both outer margins in the cervical region.

I thought we might be dealing with a Ludwig's angina or a thyroiditis, but the patient had no voice changes whatever. She had no difficulty with her tongue. The larynx showed no evidence of acute œdema. In view of the history of the case, we warned the mother that we might have to do a tracheotomy during the night. Aureomycin intravenously was ordered despite the fact that she had no temperature. The child had a good night but in the morning she suddenly clutched her throat, became very cyanosed, leaped out of bed and collapsed at the door of her room. By the time the nurse got her

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