Results

Three experiments were valueless, as blockage of the needle occurred and no readings could be obtained. Of the remaining 17, 11 developed a high, measurable internal pressure, whilst one developed enough pressure to rupture the bone end-plate, and no internal pressure was therefore measured. This disk had been cut with a very thin end-plate, and a complete transverse fracture of this developed, with protrusion of the swollen nuclear material. Simultaneously a disk from the same subject developed a pressure of over 80.2 cm. Hg. It was impossible to raise the mercury reservoir high enough to depress the mercury in the manometer to its normal level, and if the movements of reservoir and manometer meniscus are proportional then a pressure of approximately three atmospheres had developed.

The most significant result obtained was the spontaneous rupture of the annulus fibrosus in one specimen, which developed after 17 hours' immersion in water to which hyaluronidase had been added. At the time of rupture a pressure of 20 cm. Hg was measured, but, despite the production of the rupture, the internal pressure had increased to 80 cm. after eight hours' immersion. The disk bulged extensively, and, on section, the rupture of the annulus and herniation of the nucleus were easily demonstrated.

Two disks from very old subjects registered no rise of pressure, the nuclei being small, brown, and dry on section. Evidently no fluid had been absorbed, and this can be explained by the operation of two factors: (a) decreased permeation as a result of sclerosis of the end-plate; and (b) loss of polysaccharide, which occurs with advancing years.

There is little doubt that a large contribution is made by the latter factor. The absence of water absorption and change of internal pressure in disks of aged subjects is consistent with the known decreased incidence of disk prolapse in that age group. If the polysaccharide content of the nucleus is very much reduced, then fluid absorption, and therefore increase of internal pressure, will be minimal or absent and the potentiality of disk herniation reduced. Sylven (1951), using metachromatic staining methods, showed that the mucoid element in the nucleus was reduced with advancing degeneration. During the course of x-ray diffraction studies of intervertebral disks we have obtained confirmatory evidence of this (Happey, McRae, and Naylor, 1953). *In vivo*, where there is a compression force due to the superimposed body weight, a smaller absorption of fluid would lead to the development of considerable internal pressure.

A compression force was applied to disks, placed in the apparatus previously described, by means of a flat steel bar, weights being added to its ends. With the dry disk a gradual addition of weight was accompanied by a rise of internal pressure, except in those which showed advanced degeneration. The latter had lost their elasticity, and compression caused no rise of internal pressure, while subsequent immersion during maintenance of pressure was without effect. In contrast, a disk from a subject aged 35, compressed by a load of 24 kg., showed a rise of internal pressure from 47 to 119 cm. after immersion in water. Preliminary experiments in which absorption from one or both end-plates is blocked suggested that the fluid reached the nuclei by permeation through the end-plate.

Discussion

The preliminary experiments show that a high pressure can be developed within an intervertebral disk by absorption of fluid, this most probably entering through the bony end-plate. It is postulated that the possible sequence of changes leading to the development of the disk syndrome consists of: (1) depolymerization of the polysaccharides of the collagen-polysaccharide complex in the nucleus pulposus, leading to (2) increased power of water absorption, causing (3) absorption of fluid by the nucleus, the fluid

entering via the end-plate; (4) increase of pressure within the disk. The forces developed by leverage and muscular action would augment this.

It is possible that a return to the *status quo* by a process of polymerization does not occur, but that the internal pressure falls to normal as the depolymerized molecules are absorbed. This process can be repeated with each episode of symptoms, and would explain the gradual development of degenerative change in such disks. A stage is ultimately reached when the disk has degenerated to such an extent—and thereby lost its water absorption power—that prolapse cannot occur. It is possible that a similar process in multiple disks produces attacks of "fibrositis."

Further and more extensive experiments are being conducted to investigate this hypothesis, using modified apparatus to measure the high pressure generated within the disk.

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Medical Memorandum

Thyrotoxicosis Complicated by Thrombocytopenic Purpura

The association of thrombocytopenic purpura with a toxic goitre is rare. The literature reveals approximately twelve such cases (six female and six male). In several the clinical picture may have been complicated by the administration of myelotoxic drugs (Jackson, 1931; Corson, 1942; Fewell *et al.*, 1950; Hart, 1951). In the remainder no such complicating factor is evident (Finochietto *et al.*, 1936; Lavastine and Cachin, 1940; Woodruff, 1940; Bomford and Rhoads, 1941; Bicknel and Dicker, 1942; Conklin and Shank, 1944; Roberts, 1948). In the following case associated drugs, such as bismuth, "sedormid," or thiouracil, were not given before the occurrence of the purpura. The purpuric manifestations were associated with the thyrotoxicosis before treatment. Propylthiouracil was administered pre-operatively after the combination of the two diseases had been noted.

CASE REPORT

A woman aged 62 was admitted to hospital on September 5, 1951. She had been breathless on exertion for years, but this had been aggravated after a three-weeks period in bed for generalized joint pains in January, 1951. Ten days before admission a slight cough and a mild tonsillitis developed. A small haemoptysis occurred with the onset of the cough. Blood had been passed per rectum, and a widespread purpuric rash had developed over the body and limbs and in the mouth. She had bruised very easily and had lost weight over the past year. A mild degree of ankle oedema had been present for years. She had had a right-sided pneumonia with pleurisy forty years before, and several attacks of tonsillitis since. There was no history of rheumatic fever and no relevant family history.

Physical examination revealed a cachectic-looking patient who was dyspnoeic. The mucous membranes were pale, the teeth were decayed, and a mild bilateral tonsillitis was evident. Tremor was marked. The hands were warm and moist. The thyroid gland showed a generalized enlargement of both lobes. Multiple purpuric spots were apparent all over the body and on the gums and tongue. Pulse rate 90. Rhythm regular. The apex beat was displaced laterally. On auscultation the grade II apical systolic murmur was heard and crepitations were present at the bases of both lungs. There was a mild degree of ankle oedema. The liver

was enlarged and the spleen was easily felt. The blood pressure was 160/75. The haemoglobin was 29%, red cells 2,000,000 per c.mm.; the white-cell and differential counts were normal. No platelets could be seen. The bleeding-time was 14 minutes, clotting time 5 minutes, and prothrombin time 94% of normal.

On the day after admission more blood was passed per rectum, and her condition was deteriorating; she was therefore transfused with 4 pints (2.3 litres) of blood, with much improvement. The haemoglobin rose to 50%, and a platelet count six days after admission was 180,000 per c.mm. A marrow biopsy was normal; the leucocyte:erythrocyte ratio was 6:1; megakaryocytes, normal in number, showed no obvious morphological abnormality.

A week later her condition deteriorated. New petechiae appeared over the trunk. The bleeding-time had risen to 20 minutes, and the platelets had fallen to 70,000 per c.mm. and the haemoglobin was 54%. During the next week her condition fluctuated, with a tendency to improve. From the twenty-fifth day until discharge, 36 days after admission, progress was maintained, the haemoglobin rising to 76%, and the platelet count to 186,000 per c.mm.

A culture from the throat revealed no pathogenic organisms. Thyroid metabolism, estimated by radio-active iodine tests, showed results which were consistent with a moderate thyrotoxicosis. Blood cholesterol was 121 mg. per 100 ml. An electrocardiogram showed the pattern of left ventricular strain. A skiagram of the chest revealed signs of old tuberculous infiltration at the right apex. Liver-function tests were all normal. Propylthiouracil therapy was started twelve days after admission, in doses of 50 mg. three times a day. In addition penicillin was given for the tonsillitis, with iron and vitamins for the anaemia.

When seen in the out-patient department on November 1 she was still showing signs of early heart failure, and there had been a recurrence of the purpura. She was still taking propylthiouracil.

She was readmitted to hospital on November 5, showing very much the same clinical picture as before, but to a less degree. She was dyspnoeic and pale. The thyroid gland was more enlarged than previously. The hands were moist and tremor was marked. There was widespread purpura, especially on the legs. The haemoglobin was 62%, with 4,000,000 red cells per c.mm. The white-cell and differential counts were normal. The platelet count was 165,000 per c.mm. The blood cholesterol had risen to 160 mg. per 100 ml. Partial thyroidectomy was decided upon to control the thyrotoxicosis. The petechiae gradually cleared, and, apart from an epistaxis and a small subconjunctival haemorrhage into the left eye, the patient was relatively well. Propylthiouracil therapy was continued up to the time of operation, the dose having been doubled.

A partial thyroidectomy carried out one month after the second admission was uneventful. She had a mild pyrexia for four days after this. A little extra bruising of the neck occurred around the wound, but there was no fresh attack of purpura. Auricular fibrillation supervened for four days after the operation, normal rhythm then being resumed without treatment. The thyroid gland, which was large and fleshy, showed, on section, changes characteristic of toxic adenoma, modified by thiouracil.

The patient was discharged from hospital forty days after her second admission. The haemoglobin was then 86%, and the platelet count 170,000 per c.mm. She had gained 9 lb. (4.1 kg.) during the second admission period and looked fit and well.

COMMENT

The association of thrombocytopenic purpura with certain endocrine disturbances is not uncommon. Numerous authors have reported this association with pregnancy. Minot (1936) and Pohle (1939) showed that thrombocytopenic purpura may occur in certain phases of the menstrual cycle. In the above case thrombocytopenic

purpura complicated thyrotoxicosis, and there is no suggestion in the history of any other intoxication, such as from myelotoxic drugs. So far as can be ascertained, the thyrotoxicosis preceded the purpura. The incidence of the combined diseases seems to be about equal between male and female. No case has occurred below the age of 28. Probably the total number of cases reported of the combined diseases, without any complicating factor, is less than ten. Wintrobe (1946) believes that there is no adequate reason to assume that the combination represents more than the coincidence of two unrelated diseases. The paucity of cases lends some support to this opinion. On the other hand, Woodruff (1940) takes the opposite point of view, and believes that the leucocytes and platelets are specifically affected by the thyrotoxic state. He believes that the degree of toxæmia produced may either stimulate or depress the number of platelets, according to the mildness or severity of the degree of toxæmia.

In a discussion on the cause of idiopathic thrombocytopenic purpura, Robson (1949) suggests that the spleen and other reticulo-endothelial tissues produce some factor which alters the state of the capillaries and reduces platelet formation from megakaryocytes. Such might be the case here. It does seem possible that the state of capillaries was a more important factor than the thrombocytopenia, on readmission, when purpura was still evident with a platelet count of 165,000 per c.mm. It seems reasonable to suppose that the activity of the spleen might be reduced with the reduction of lymphatic hyperplasia which occurs after thyroidectomy. It was felt after readmission that partial thyroidectomy was necessary in this instance. Propylthiouracil, while having some effect on the thyrotoxic state, did not seem to benefit the purpuric manifestations. In view of the case reported by Fewell *et al.* (1950), in which purpura followed propylthiouracil therapy, it seems wiser not to use this drug when the two diseases are combined. It is suggested that operation is preferable to drug therapy when thrombocytopenic purpura and thyrotoxicosis co-exist.

Our thanks are due to Dr. Kenneth Robertson for permission to publish this case, and to Mr. L. A. Richardson, who carried out the partial thyroidectomy. We would also like to thank the laboratory for the haematological investigations, and the radio-therapeutic department for the radioactive iodine tests.

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The new radiological department of the Clatterbridge Hospital, Bebington, Cheshire, was officially opened on October 2 by Dr. Peter Kerley. The department is entirely self-contained and has been planned to give direct access to the operating theatre and easy communication with the wards. It is divided into three main sections for general and fluoroscopic work, pulmonary, cardiac, and gastro-intestinal examinations, and for genito-urinary investigations.