Summary

The age-and-sex distribution of atheroma and stenosis of the carotid and vertebral systems in 93 unselected necropsies is described. Attention is drawn to the frequency with which lesions occur in some sites, and possible reasons for this are discussed.

The relationship between neck-artery stenosis and aortic atheroma, and also the strong correlation between stenosis in the four neck artery systems, are described.

The relationship between strokes and neck-artery stenosis, ulceration, and occlusion, is discussed.

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ACUTE MYXOEDEMA PRECIPITATED BY PNEUMONIA

REPORT OF FIVE CASES

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It seems to be generally unknown that myxoedema may have a sudden onset in seemingly healthy individuals. Search of the literature has not produced any well-substantiated cases. Watney and Douthwaite (1932) described the case of a woman of 63 whose first symptoms of myxoedema began in December and who was almost in myxoedema coma when seen by them the following February. Lloyd (1933) reported the case of a woman aged 55 who was said to have been in perfect health in August, but when seen by him in October presented a typical picture of myxoedema. Means (1948), quoting these two cases, comments: "Our guess is that these cases were not actually more acute than others, but that the apparent acute onset was the final blossoming of a picture which must have been present, although unnoticed, for a longer period." Asher (1955) states: "Myxoedema is a chronic rather than acute disease, and therefore rarely presents with a crisis. It only does so when the disease has progressed to a very advanced stage, or if an acute complication develops."

In the past two years we have jointly observed three cases of severe myxoedema of very rapid onset, apparently precipitated by pneumonia, and two similar

cases were previously seen by one of us (W.H.). One of these cases has been reported in a different context (Le Marquand, Hausmann, and Hemsted, 1953). We are concerned, therefore, with five patients who appear to have developed acute myxoedema as a result of pneumonia.

Case 1

A man aged 60 was well and working until three days before his admission to hospital, when he became confused and lethargic. He had no cough or pyrexia. His doctor detected an area of dullness in the left chest, swelling of the face and neck, and suspected carcinoma of the lung with cerebral metastases and mediastinal obstruction. On admission (February 25, 1959) he was pale and myxoedematous in appearance. His mental reactions were slow and he had marked oedema of the face and legs. X-ray examination of the chest showed enlargement of the heart and left-upper-lobe consolidation, which a few days later spread to the right lower lobe. An electrocardiogram showed low voltage of QRS in standard leads and inversion of T waves in leads I, aVL, V₃, and V₅. Radioiodine uptake test gave very low normal values verging on mild hypothyroidism. Serum cholesterol was 295–365 mg./100 ml.

He was treated with penicillin, streptomycin, and thyroxine and slowly lost his extensive oedema, though some of the myxoedematous appearance remained. Cardiographic tracings returned to normal after three weeks' administration of thyroxine, on which he has since been maintained in good health. A follow-up chest film showed a heart of normal size and complete clearing of both lung fields.

Comment.—In this case acute myxoedema was provoked by pneumonia which, though clinically and radiologically extensive, was practically symptomless.

Case 2

A woman aged 52 gave a week's history of right-sided pain in the chest with productive cough and slight pyrexia. For the previous two years she had been tired and received iron tablets for anaemia from her own doctor. Her husband was admitted to hospital five days earlier with severe pneumonia. On admission (April 11, 1959) her appearance was clearly myxoedematous. Speech and reactions were slowed down and there was marked oedema of the face and legs. The temperature was 99.4° F. (37.4° C.) and she had physical signs of extensive right-upper-lobe pneumonia. X-ray examination of the chest showed an enlarged heart with consolidation of the posterior segment of the right upper and right middle lobes; further films suggested fluid at the right base. Serum cholesterol was 380 mg./100 ml. and haemoglobin 71%. The electrocardiogram showed bradycardia, low voltage, and T-wave inversion consistent with myxoedema. Radioiodine uptake test showed "low normal thyroid activity; thyroid leg ratio consistent with hypothyroidism."

She was treated with penicillin, streptomycin, thyroxine, and chlorothiazide, and made a very slow recovery. Eight weeks later her lung fields were radiologically clear and the size of the heart was reduced, but cardiographic tracings still showed low voltage. After three months her heart was of normal size, the electrocardiogram normal, and haemoglobin 90%. Since then she has remained in very good health on a maintenance dose of thyroxine.

Comment.—This patient had few systemic symptoms and low pyrexia in spite of very extensive pneumonia. Her two years' history of lassitude and anaemia suggests the possibility of pre-existing mild hypothyroidism, with sudden deterioration under the stress of severe pneumonia.

Case 3

A woman aged 76 was admitted to hospital on December 20, 1955, in a semicomatose condition. Reaction to

questioning was exceedingly slow, movements were ponderous, her voice was husky and appearance myxoedematous. The pulse rate was 70 a minute, rectal temperature 95° F. (35° C.), blood-pressure 95/50 mm. Hg, thyroid not palpable. There was an area of dullness with bronchial breathing and coarse crepitations at the left base. X-ray examination of the chest revealed consolidation of the basal segments of the left lower lobe and some shadowing at the right base. An electrocardiogram showed bradycardia with low voltage and inverted T waves, compatible with myxoedema. The haemoglobin was 65%.

She was treated with penicillin, streptomycin, and thyroxine and made good progress. A further chest film one week later showed that the lung fields were nearly clear. She was discharged on January 17, 1956, with a haemoglobin of 80%, but was readmitted half-conscious on March 7, again following respiratory infection. She was finally discharged on a maintenance dose of thyroxine.

Comment.—In this case no reliable previous history could be obtained, but a woman aged 76, living alone, may be assumed to have been reasonably well to be able to cope with her household duties.

Case 4

This patient was a woman aged 73. We cannot do better than quote from her doctor's letter: "I have seen quite a lot of her recently while attending her husband for lobar pneumonia. She is normally pretty alert and active. When calling to see her husband to-day I was told that she had been weak and drowsy for the past two days. She spoke slowly in a deep voice and seemed confused. There was considerable oedema of the legs and around her eyes. A few hours ago she apparently had some sort of fit and was unconscious, pale, and foaming at the mouth. This lasted about 15 minutes, during which time she bit her tongue but was not incontinent. I saw her shortly afterwards, when she was pale and semicomatose. She has now improved and is rational, but speaks very slowly and in a deep voice. There is no previous history of any illness or fits, nor of any nervous trouble. Her heart sounds are of poor quality and the rate is 50 a minute. I think this must be a case of acute myxoedema."

On admission to hospital on January 22, 1958, she was comatose; the temperature was 80° F. (26.7° C.), pulse rate 56, and blood-pressure 145/80. She died 12 hours later in spite of treatment. A necropsy report (Dr. F. Hampson) stated: "The thyroid was small and appeared rather fibrosed on cut section. There was much greenish pus in the trachea and main bronchi, and beads of pus could be expressed from the cut surfaces of both lungs." The cause of death was certified as myxoedema coma.

Comment.—This is a case of outstanding interest. The patient here was actually observed by her doctor while acute myxoedema developed over a period of 48 hours. The evidence that pneumonia was the precipitating cause seems very strong: she was nursing her husband, who was suffering from pneumonia, and post-mortem findings were suggestive of bronchopneumonia or purulent bronchitis. Another striking point was the observation of an epileptic fit preceding the onset of coma; this course of events has been noted in other cases of myxoedema coma, where it usually indicated rapid deterioration and death.

Case 5

A woman aged 61, whose case has been previously reported (Le Marquand *et al.*, 1953), was admitted to hospital on January 7, 1951. She had had two episodes of left hemiplegia, in both cases followed by rapid recovery, and was in good health until two weeks before admission, when she developed a cold and a severe cough. When first seen by her doctor the day before admission she was confused. Marked oedema of the face and eyelids developed in the

next 24 hours. She died after four days. At necropsy extensive right-sided pneumonia and fibrosis of the thyroid gland were found.

Discussion

Myxoedema of rapid onset has, so far as we know, never been reported. This is in marked contrast to other endocrine deficiency states, such as diabetes mellitus, Addison's disease, and hypopituitarism, which often present with acute crises. Physiological reasons may account for this discrepancy, and observations after thyroidectomy have shown that there is usually an interval of one to two months before myxoedema becomes apparent. The most convincing evidence to this effect was reported by Gilligan *et al.* (1934), who studied 47 patients after total removal of the normal thyroid gland because of intractable heart disease or angina pectoris. They state: "After varying periods of time some of the signs and symptoms of myxoedema developed in every patient following total thyroidectomy. By the end of the first post-operative month most of the patients showed mild clinical signs and symptoms, such as dry skin, slight pallor, and sensitivity to cold. After the second post-operative month more serious symptoms of myxoedema developed in many patients, such as weakness of the extremities, drowsiness, muscle irregularity, and transient puffiness of the face, hands, and feet." It should be noted, however, that in all these cases normally functioning glands were removed, and that the position may be quite different if thyroidectomy were carried out when the thyroid was already defective.

It is our hypothesis that in the five cases reported by us the thyroid gland was already considerably damaged, and that the residue of functioning thyroid tissue was working under maximum stimulation from the thyrotropic hormone. There was therefore no clinical hypothyroidism prior to the onset of the acute illness (with the possible exception of Case 2), but these patients had no reserve when exposed to severe stress. We believe that this is the probable explanation of the course of events as observed by us.

The most important stress factor in all our cases was pneumonia, which involved more than one lobe in four of our patients, while in the fifth (Case 4), who was nursing her husband with pneumonia until two days before the onset of her illness, there was post-mortem evidence of purulent bronchitis. Another stress factor was exposure to cold; four of our cases occurred during the winter months, the fifth in early April. Inquiries have shown that the first 10 days of April, 1959, were exceptionally cold compared with the previous two years, that humidity was unusually high from April 4 to 10, and that notifications of pneumonia during the first half of April were higher than usual.

We have no evidence that pneumonia as a stress factor stands in any specific relation to the thyroid gland and that other stresses may not lead to similar results, but we feel that, in this country at least, pneumonia and exposure to cold are the two major influences.

It is true to say that as none of these patients was investigated prior to admission the evidence for the acuteness of the onset of myxoedema is not conclusive; it is certainly very strong in Case 4, where the patient was actually observed by her doctor while myxoedema developed over a period of 48 hours. It is also strong in Cases 1 and 5, where the patients were thought to be quite normal before the onset of pneumonia. Of the

remaining two cases all we can say is that thyroid function, perhaps already inadequate in Case 2, deteriorated acutely with the onset of infection, while in Case 3 no previous history was available but the patient became rapidly comatose with the development of pneumonia.

A final point of interest was the contrast between the relative lack of symptoms and the evidence of extensive consolidation in four of our five patients. We think that the silent character of these severe infections is a matter of significance which needs stressing, and that attention should be drawn towards the possible presence of myxoedema when faced with pneumonia with minimal symptoms.

Summary

Five cases of myxoedema of acute onset, including one new case of coma, are reported. The stress factors were severe pneumonia and exposure to cold. It is suggested that in all these cases there was a sudden breakdown of function in potentially inadequate thyroid glands, already working at maximum capacity to meet normal requirements. As the pneumonia caused few symptoms in all our patients it was liable to be overlooked.

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The Second British Congress on the History of Medicine and Pharmacy was held in London from September 27 to 29. It was organized by the Faculty of the History of Medicine and Pharmacy of the Worshipful Society of Apothecaries of London with the co-operation of the Chemical Society. The subject chosen for discussion was "Chemistry in the Service of Medicine," and papers were read at the Apothecaries' Hall, at the Royal College of Physicians, at the Royal College of Surgeons, and at the Chemical Society, Burlington House. At a brief ceremony during the Congress the chairman of the Faculty, Dr. W. S. C. Copeman, conferred the Faculty's honorary fellowship on Professor K. J. Franklin, F.R.S., distinguished physiologist and medical historian, and on Dr. Ernst Wickersheimer, president of the Société Internationale d'Histoire de la Médecine and a leading historian of medicine in France. During the Congress a dinner was held in the hall of the Worshipful Society of Apothecaries. The guest of honour was Sir Howard Florey, P.R.S., and the president of the Chemical Society, Sir Alexander Todd, F.R.S., gave an address. Sir Alexander discussed the long-standing relation between chemistry and medicine, and stressed that medicine and the search for health had provided a great stimulus to chemical research. He foresaw the day when the accepted separation of the basic sciences would have to be broken down. At present the range of skills for tackling a research problem comprehensively could probably only be found in research institutes, but research could best be carried out in the universities, which must use the constant influx of young minds to cross the barriers between the sciences.

NUCLEAR SEXING WITH ACETO-ORCEIN

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Nuclear sexing, which stems from the discovery of sexual dimorphism in interphase nuclei (Barr and Bertram, 1949), is now accepted as a routine clinical diagnostic test (Lennox, 1956; Davidson, 1960). The oral-mucosal-smear method (Moore and Barr, 1955; Marberger, Boccabella, and Nelson, 1955; Klinger and Ludwig, 1957) has gained wide popularity because specimens may be obtained with minimal inconvenience to the patient. The present paper describes the application of the aceto-orcein squash technique to oral mucosal smears. It is just as accurate as other methods but much more rapid, and it has the additional advantage that fine details of nuclear structure are more readily revealed by squashing and flattening the freshly obtained cells.

Materials and Methods

Stains

Orcein may be used with or without lactic acid.

Stock Solution.—Synthetic orcein, 1 g.; glacial acetic acid, 45 ml. Boil, cool, and filter.

Simple Aceto-orcein.—Dilute 45 parts stock solution with 55 parts distilled water and filter. Periodic filtration is necessary.

Lacto-aceto-orcein.—Dilute 50 parts stock solution with 50 parts of 70% lactic acid and filter.

Fresh Preparations

An oral mucosal smear is obtained by scraping the inside of the patient's cheek with a wooden spatula. Several short vertical strokes are made with firm pressure, and the desquamated cells and saliva are then scooped up on the end of the spatula and spread on the surface of a clean dry slide. One drop of stain is quickly placed on the centre of the smear and a thin coverglass— $\frac{7}{8}$ in. (22 mm.) square or $\frac{7}{8}$ by $1\frac{1}{2}$ in. (22 by 38 mm.) rectangle—is laid over it. One or more layers of filter paper are placed on top and the coverglass is pressed down by drawing the thumb across from one end of the slide to the other. To avoid moving the coverglass on the slide the filter paper is firmly held down over one corner of the cover with the left hand while the right hand moves across from left to right. The filter paper absorbs excess stain expressed from below the coverslip. With insufficient pressure the nuclear membrane is wrinkled: with correct pressure the nuclei are evenly flattened. Extrusion of the nuclei from the cell is not disadvantageous provided that the nuclear membrane remains intact. With simple aceto-orcein they should be stored in a covered tray in a refrigerator and fresh stain added to the edge of the coverglass to prevent drying out. The hygroscopic lactic acid in lacto-aceto-orcein