Discussion

The bone dystrophy of myopathy has in common with the muscular weakness only one undisputed aetiological factor, which is a heredo-familial incidence (Schultze, 1899; Dreyer, 1906; and others). Spiller (1898) assumed a process taking place in myopathy which caused atrophy and developmental arrest in early life, probably involving bones as well. Hemiatrophy, a condition which one attempts to explain by an incomplete minimal form of twinning (Gesell, 1921), does not appear to be related, as the myopathic bone dystrophy may involve bones in an asymmetrical manner. It is hardly surprising that abnormalities of the sympathetic nervous system (Kur *et al.*, 1936), endocrine system, or diencephalon (Zellweger, 1946) have been invoked to explain the puzzling combination of bone and muscle dystrophy.

Friedreich, in describing a case of an 18-year-old youth, postulated an external concentric progressive bone atrophy with simultaneous deposition of new bone along the medullary surface of the cortex. He considered the process to be a nutritional atrophy rather than an arrest in development.

Despite the numerous points of similarity between this humerus and one whose development has been arrested or slowed down by paralysis—for example, acute anterior poliomyelitis—it is not easy to explain all characteristics by disuse in the absence of any osteoporosis in this case. Even the versatility of Pommer's (1925) theories of tissue pressure as a basis for the mechanism of changes in blood supply causing relative preponderance of osteoclastic or osteoblastic activity does not provide a ready explanation of why the bone should be abnormally slender and of normal density in this case. If these bones have ever been of normal dimensions the present appearances must be due to the process postulated by Friedreich. Even if the bones have developed in this fashion (never having been normal) the compactum must partially, at least, have been laid down from within in order to explain the alterations in cortex/medullary ratio. Nevertheless, the final result in this condition, as in poliomyelitis, is in striking contrast to the thick sturdy bone with prominent muscle attachment produced by continued heavy muscular stresses. It would be impossible to assess whether developmental arrest had occurred from the time that muscular weakness became evident in this case; the question could be answered only by repeated observation of progressive cases beginning at an early stage.

Trophic changes are not operative in the same sense as they are in tabes when kinaesthetic sensation is commonly involved and Charcot's joints occur, although the word "trophic," meaning a nutritional change, would be applicable.

Apart from recognizing familial incidence in both muscle and bone changes, we feel that there is little to be gained by theorizing upon the pathogenesis of the bone changes.

Summary

A case of myopathy showing atrophy and hypoplasia of humerus and scapula is described. Previous literature is reviewed and possible mechanisms are briefly discussed.

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A CASE OF PRIMARY AMENORRHOEA ASSOCIATED WITH ASTHMA

BY

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The Physiology of Primary Amenorrhoea

The mechanism responsible for menstruation may be interrupted at three levels: first, the output of pituitary gonadotrophins may not suffice to stimulate the ovary to secrete oestradiol, to ovulate, and to secrete progesterone; secondly, the ovaries may be unable to respond to a normal pituitary gonadotrophic stimulus; and, thirdly, the uterus may not respond to the ovarian hormones. Primary amenorrhoea may arise at any of these levels. Pituitary deficiency may be of all degrees from the extreme of pituitary dwarfism, through decreasing grades of gonadotrophic hypoplasia, to a mere delay in the establishment of puberty and menstruation. Ovarian deficiency similarly ranges from complete agenesis to the mildest hypoplasias. An infantile uterus is only rarely seen when ovarian secretion is normal, but undue delay in the establishment of menstruation may leave the uterus irreversibly infantile.

There is little hope of curing primary amenorrhoea if an infantile body-build indicates severe pituitary hypoplasia, or if extreme ovarian deficiency is shown by a eunuchoid body-build (hormonal castrate). Success is most likely in the obese type of young woman who may perhaps be regarded as having no more than a very undue delay of puberty.

Primary amenorrhoea may be treated by either ovarian or pituitary hormones. At the lowest level intermittent oestrogen therapy will very often induce cyclical withdrawal haemorrhage from the uterus. Such bleeding may give psychological benefit, but is too far removed from the normal mechanism of menstruation to induce a normal pituitary-ovarian rhythm. Better results follow when progesterone succeeds the oestrogen—for example, oestrogen for five days, progesterone for five days, and 20 days' rest. Bickers (1948) induced cyclical bleeding by this means in 60% of cases of primary amenorrhoea, and in 40% menstruation continued for at least three months after stopping treatment.

The most logical treatment of primary amenorrhoea, however, is to stimulate or reinforce the normal pituitary secretion of follicle-stimulating and luteinizing hormones. Suitable cases often respond to massive

doses such as five daily injections of 3,000 i.u. of serum gonadotrophin followed by three injections of 1,500 i.u. of chorionic gonadotrophin on alternate days (Riisfeldt, 1949). The treatment may, however, be interrupted either because antihormones to the serum gonadotrophin form or because the patient becomes allergic to other components of the mare's serum. The proprietary preparation "synapoidin" avoids this difficulty by combining chorionic gonadotrophin with a "synergistic" pituitary extract; the preparation is said to exert both follicle-stimulating and luteinizing effects, and encouraging results in the treatment of amenorrhoea of pituitary origin were reported by Davis (1944).

Either form of pituitary therapy may sometimes excessively stimulate the ovaries. The patient suffers severe abdominal pain and the ovaries are greatly enlarged by cystic changes, with haemorrhages into cysts and interstitial tissue. The ovaries invariably return to normal within three weeks of stopping treatment (Movin, 1949).

Allergy and Menstruation

The association of ovarian and especially of menstrual disorders with allergic manifestations has often been noted. Thus, cases of skin hypersensitivity which vary with the stage of the premenstrual cycle are not infrequently observed, and premenstrual and menstrual migraine are also well-known entities. The association of asthma and menstruation is perhaps less well known, but certain well-defined groups occur. First, there are those children who have asthma till the age of puberty and who at the menarche are completely cured or much improved (these are often said to have "grown out of it"), and as many as one-third are completely free of attacks. Then there are women whose asthmatic attacks are predominantly premenstrual in a well-defined manner, and these attacks are completely relieved at the onset of the flow. Others have their attacks regularly during the flow, while some have attacks which appear haphazardly at any time during the month. Often patients are free from attacks during pregnancy—so much so that it has been alleged that attacks resembling asthma in the pregnant woman cannot be accepted as being genuinely asthmatic and should be regarded as hysterical (Curschmann, 1920). This freedom from an allergic manifestation during pregnancy is very similar to, and is probably on the same basis as, the temporary remissions of various skin allergies, hay-fever, and migraine; and of rheumatoid arthritis. At the menopause, again, some women are relieved, but others definitely deteriorate.

The endocrine basis of a certain proportion of cases of asthma in the female cannot be doubted—even less so nowadays when we learn that A.C.T.H. (Astwood *et al.*, 1950) and cortisone (Carrier *et al.*, 1950) can be used to relieve asthmatic attacks. The mechanism is not yet understood, but the result may be due to alteration in water, salt, or carbohydrate metabolism, or to modification of histamine and acetylcholine activity. Possibly also there may be some modification of neural mechanisms via the hypo-

thalamus. Thus Introzzi and Larizza (1947) achieved good results in the treatment of bronchial asthma with folliculin, which they claim modifies the tonus of the vegetative nervous system.

Case Report

A. The Respiratory History

A girl first attended the London Chest Hospital in August, 1937, when aged 17. She gave a history of two weeks' dyspnoea of sudden onset, with sweating, wheeziness, and cough with purulent expectoration; the cough was troublesome by day, and the wheezing was cleared by coughing. Her dyspnoea was severe enough to necessitate her being propped up at night. Her only previous chest history was of an attack of bronchitis lasting two weeks when she was 14. She was small for her age and intelligent. Examination of the chest revealed numerous rhonchi scattered in both lungs, and crepitations at both bases. A radiograph of the chest showed the heart slightly deviated to the left, and the right lung field more radiolucent than the other. It was thought that the right lung was emphysematous, thus pushing the mediastinum over. Screening confirmed the appearance of pulmonary emphysema, the right dome moving little and being depressed and flattened. The heart was displaced to the left on expiration and became more central on inspiration. Mist. lobel. co. and ephedrine were given.

The patient was admitted for investigation. Bronchoscopy showed no abnormality; a right bronchogram revealed a normal bronchial tree, and the sputum was negative for tubercle bacilli. Bencard skin tests were negative for groups A1 and A2. She continued to complain of dyspnoea, which was not related to exertion, but came on many times daily while she was at rest. By June, 1938, she had improved considerably, but had a recent recurrence of dyspnoea, especially when she walked.

B. The Menstrual History

Meanwhile the patient had also been attending the London Hospital on account of the retarded development of secondary sex characters and failure to menstruate, and a report suggested that this delayed puberty was due to her poor general condition. She continued to attend right through the latter half of 1939 and the early part of 1940, with varying response to treatment. She was seen again in April, 1943, when it was reported that she had not worked for three years, that she had remained short of breath but had not been too bad until lately, and in addition had had a sharp pain and an intermittent dragging sensation on the left side. Examination showed that there had been no change in the general bodily size or contour. Physical signs of emphysema on the right and numerous rhonchi on the

Chart showing courses of synapoidin and uterine bleeding in primary amenorrhoea.

left were found. An E.C.G. was of low voltage in Lead I, but otherwise the curves revealed no significant abnormality. Breathing exercises brought some benefit, but she relapsed in September, 1943. Rhinorrhoea and sneezing also developed. An E.N.T. report stated that she had the pale type of nasal mucosa often found in asthmatics. Nasal ephedrine drops considerably relieved her.

The patient was first seen by me in October, 1943, when she was 24. Her complaint was of severe asthma, and she had never menstruated. On examination she was pale and looked younger than her age. Her breasts were only slightly developed, being of the type generally seen in girls at the onset of puberty, and her external genitalia were infantile. There was no pubic hair and only slight axillary hair. Pelvic examination revealed an undeveloped cervix and a very small uterus.

The asthma continued unchanged in spite of all the usual palliatives, and in March, 1945, was severe enough to necessitate adrenaline injections. In September, 1945, stilboestrol, 0.5 mg. daily, was started, and by December, 1945, the patient was sufficiently improved to wish to start work. The daily stilboestrol was continued until December, 1947, when the dose was increased to 1 mg. daily. There was slight enlargement of her breasts.

In August, 1948, she was seen by Mr. Leonard Phillips, who advised a course of synapoidin. The size and spacing of the injections given is shown in the accompanying chart. The first 10 injections were followed by uterine haemorrhage lasting for eight days, the first menstrual period of the patient's life, at the age of 29.

By September, 1949, after eight courses of synapoidin and six periods, the cervix was definitely larger and softer and the uterus was a little larger. In April, 1950, the labia were quite normal and the uterus definitely larger. In October, 1950, the labia majora were fully developed and the labia minora were normal. The cervix was that of a normal adult, but the uterus was still small. The breasts were well developed, with prominent nipples and deeply pigmented areolae. A vaginal smear showed an adult type of keratinized epithelium. Treatment with synapoidin is continuing successfully.

The patient attended the London Chest Hospital for review in December, 1950, when she was able to report that she was much better than ever before, her breathing was easier, there was no cough or sputum, and instead of taking four or five $\frac{1}{2}$ -gr. (32-mg.) tablets of ephedrine daily she was now able to continue comfortably with two or three tablets a week.

Summary

A case of primary amenorrhoea with severe asthma is described. The use of endocrine therapy has resulted in the development of secondary sex characters and the establishment of irregular menstruation, and simultaneously there has been considerable improvement of the asthma. Continued treatment may induce a true puberty with regular menstruation. As the patient is now 30 years old this may be very difficult, but the result so far has been most promising. Probably the improvement in the asthma is comparable to that noted in children at the time of puberty.

My thanks are due to Mr. Leonard Phillips for his advice and opinion; to Dr. N. Lloyd Rusby for giving me access to case notes at the London Chest Hospital; and to Dr. Martin Hynes for his encouragement and assistance with the microscopical examination.

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THE ALBUMIN ANTIBODY IN ROUTINE RHESUS GROUPING ADAPTATION OF THE CHOWN CAPILLARY METHOD

BY

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Attention has been drawn in recent months to the difficulty experienced in maintaining adequate supplies to laboratories of Rhesus testing serum, especially anti-D. This difficulty has arisen from the increasing tendency to screen for this factor *all* expectant mothers and patients requiring blood transfusion. For these tests serum containing the complete or saline antibody is generally used, and the examination is carried out by the tube method. It is unfortunate that the blood of mothers of erythroblastotic infants usually shows a comparatively low titre of this antibody; more often the serum contains the incomplete or albumin antibody in high titre. It would appear that if this latter antibody were in general use the supply problem would be solved.

In the laboratory of the North Middlesex Hospital we found that the albumin antibody is suitable for routine screening, using the Chown capillary technique in which a saline suspension of the unknown red cells is allowed to fall through a column of serum containing the Rh antibody in a capillary tube. This tube is inclined at an angle of 45 degrees against an illuminated glass screen, the light source being so disposed as to give a fairly constant temperature of 37° C. across the screen face. The Rh-positive cells agglutinate into clumps which are readily seen with the naked eye, spaced in the length of the fluid with clear intervals between each, whilst the Rh-negative cells fall evenly to the bottom of the capillary type, leaving a clear supernatant fluid. This method combines the advantages of economy of serum and effort with rapidity, the positive results being apparent in 5-15 minutes, and it has been used exclusively in that laboratory since routine Rhesus screening was introduced in December, 1947, and from October, 1949, the albumin antibody has replaced the saline antibody formerly employed.

In the hands of some workers the Chown test seems to be a little difficult, but by rigidly adhering to the details of the technique as originally set out (Chown and Lewis 1946) no difficulty has been encountered by us and, furthermore, technicians become familiar with it after a few demonstrations.

To use the albumin antibody a few minor modifications of the original method have been evolved.

Apparatus.—The apparatus used is the box as described by Chown.

Capillary Tubes.—These are pulled from ordinary glass tubing similar to that used for making Pasteur pipettes. The internal capillary diameter should be about 0.5 mm. and the length about 8 cm.

Serum.—The serum containing the albumin antibody is diluted with an equal volume of 20% bovine albumin. Dilution with weaker albumin solution (15% or 10%) gives satisfactory results, but these take longer to appear, often 30-40 minutes, thus depriving the method of one of its advantages. The speed of the reaction is also affected by the titre, 1:8 being regarded as the lowest satisfactory for general use.