115 mg. daily at the 35th week. We suggested in our previous paper that the essential therapeutic mechanism may have been the same in our series of cases as in that of Smith—namely, that we were providing extrinsically the progesterone which was intrinsically lacking in these cases of early habitual abortion, whereas Smith was stimulating, by means of extrinsically administered oestrogen, the secretion of placental hormones and especially progesterone.

It may be observed that the dose of progesterone administered by implantation appears to be small. It has not been easy to determine the rate of absorption of implanted progesterone, because the pellets are apt to extrude if implanted superficially. Bishop and Folley (1951) were able to study the rate of absorption of only four pellets of 50 mg. of progesterone implanted in female patients, and found that 40% of each pellet was absorbed in just over 40 days. This indicates, for what it is worth, that progesterone is one of the more rapidly absorbed hormones when administered by pellet implantation. Calculating from the findings of Bishop and Folley, we think it probable that the long cylindrical-shaped 25-mg. pellet which we have been using is fairly rapidly absorbed and may not remain effective for more than about a month. Nevertheless, if these early habitual abortions are due to a progesterone deficiency which operates during the second and third months of pregnancy, possibly by leading to an inadequate decidual reaction which endangers the safe embedding of the early ovum, administration of a constant though transient exogenous supply of progesterone by implantation may carry the patient over the critical period when abortion is mostly likely to occur.

One is of course always conscious of the possibility that the particular pregnancy under consideration may have gone to term without therapeutic aid. It is for this reason that we sought statistical advice both in regard to our original series and in respect of the present series. (Dr. Doll again is of the opinion that our results are of significance provided that the incidence of true habitual abortion is not much less than 0.1%.) One cannot, however, altogether exclude the psychological factor. Many habitual aborters and their husbands or relatives are highly strung and need reassurance that all will be well in the present pregnancy. Possibly the psychotherapeutic effect of an implant, as opposed to a series of injections or tablets by mouth, may in some cases supply the necessary confidence to enable the patient to retain the embryo during those early critical days.

Bevis (1951) has studied a series of 32 cases of habitual abortion (three or more previous abortions), of which 26 (81%) gave birth to live children. These patients received no treatment which we would regard as effective, though they were advised to rest at the time the menses would have been due. They were, however, submitted to elaborate investigation, including glucose-tolerance tests, estimation of basal metabolic rate, and fortnightly estimation of urinary pregnanediol. It is true that some of Bevis's cases did not come under observation until the 12th week of pregnancy—that is, when the early abortion hazard had been overcome. Nevertheless, if one is to accept his results at their face value—and we are in no position to say that one should not—and if one is also to agree with the calculations of Eastman and Malpas, one must logically conclude that 81 minus 16%—namely, 65%—of patients who have experienced more than three early abortions have done so for psychological reasons and that any procedure which is likely to gain their confidence may well prove successful. There is of course an obvious way of settling the question whether a progesterone implant is endocrinologically or merely psychologically therapeutic—namely, to treat alternate cases with implants of progesterone and an inert compound such as cholesterol.

We would, however, repeat the observation which we made in our first paper, that our results do not indicate that progesterone-pellet implantation in the dosage used is harmful in cases of habitual abortion.

Summary

A further series of 40 cases with a history of two or more miscarriages before the end of the fifth month of pregnancy, immediately preceding the treated pregnancy, were given an implantation of six 25-mg. pellets of progesterone.

Previously a series of 45 cases was reported upon. From this combined series of 85 cases 32 patients had experienced at least three miscarriages occurring before the end of the fifth month of pregnancy. Twenty-three patients (72%) produced live children during the current pregnancy in which the progesterone-pellet implantation was performed. This represents a significantly higher success rate than that expected from the calculations of Malpas and Eastman.

The results of Bevis (80% success rate with three or more previous miscarriages) in patients who received no effective endocrine therapy but were submitted to a series of elaborate investigations are discussed in the light of the possible psychotherapeutic effect of any procedure likely to gain the patient's confidence.

We should like to record our thanks to Dr. Richard Doll, of the Statistical Research Unit, Medical Research Council, for his interest and comments on this series of cases, and to members of the staff of Chelsea Hospital for Women and to other gynaecologists and doctors who have referred the patients in this series to us for implantation.

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ACUTE POLYARTHRITIS WITH PULMONARY CONSOLIDATION AND PLEURAL EFFUSION

BY

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Although numerous examples of "rheumatic pneumonia" and "rheumatic pleurisy" have been recorded, many observers are sceptical of the specific nature of these conditions, chiefly because in most reported cases severe cardiac damage has been present. The following cases are of interest because, although the probable diagnosis was acute rheumatism with pulmonary manifestations, no evidence of cardiac involvement could be detected, although eventually a mitral systolic murmur appeared in one.

Case 1

A man aged 37 was admitted to hospital on July 1, 1950, because of a rapid deterioration in his general condition. Fourteen days before admission his knee-joints had become painful, red, and swollen, and later his ankle-joints, wrists, interphalangeal joints, elbow-joints, and shoulder-joints became similarly affected. His health had been good until December, 1949, when he had rheumatic fever; he made a complete recovery and resumed work in February, 1950. His mother, aged 67, was crippled with rheumatoid arthritis.

On admission the wrists, interphalangeal joints, knees, and ankles were red, swollen, and extremely painful and tender, and the shoulder-joints and elbows were painful on movement. The skin was warm and moist. The patient appeared gravely ill; his colour was ashy-blue, he was slightly dyspnoeic at rest, and he had an anxious expression. His temperature was 100.4° F. (38° C.), pulse 108, and respirations 22. Over the lower lobe of the left lung the percussion note was dull, the respiratory murmur bronchial and loud, and the vocal resonance increased. Numerous medium moist crepitations could be heard over the left lower lobe. Clinical and electrocardiographic examination revealed no significant cardiac involvement at any stage. His general condition began to improve on July 5. A chest radiograph on July 7 revealed left basal consolidation with overlying pleural thickening or a small effusion. The heart was of normal size. Aspiration on July 10 produced 60 ml. of a sterile, straw-coloured fluid containing roughly equal numbers of polymorphs and lymphocytes; no tubercle bacilli were found on direct examination, culture, or guinea-pig inoculation. Signs of consolidation in the left lower lobe began to disappear on July 12, and a radiograph on the 14th showed that the condition had almost cleared up; crepitations were present, however, until August 11. Cough was slight throughout, and was always non-productive of sputum.

Calcium aspirin, 150 gr. (10 g.) daily, was given from July 1 to 9, but, although it relieved joint pains, the temperature did not settle, varying between 97 and 103° F. (36.1 and 39.4° C.). Penicillin, 600,000 units daily, was started on July 9, and the temperature, which had fallen on the previous day, settled, although there were subsequent minor elevations. Penicillin was stopped on July 18. After stopping the aspirin on July 9 the joints again became swollen and painful, and it was reinstituted on July 12, with marked benefit; it was finally discontinued on September 27. Blood examination on July 4 showed: R.B.C., 5,500,000; Hb, 90%; W.B.C., 7,000 (polymorphs 82%, lymphocytes 18%); no malaria parasites; and on July 8: W.B.C., 6,500 (polymorphs 78%, lymphocytes 20%, monocytes 2%); no malaria parasites. Blood cultures on July 10, 11, and 13 were negative.

A throat swab on July 6 was negative for *B. diphtheriae* and haemolytic streptococci; there was a predominant growth of *Str. viridans* and a light growth of pneumococci. Serological tests on serum taken on July 13 were negative for typhoid fever, paratyphoid A and B, brucellosis, and typhus. Serum taken on August 29 was tested at Colindale Virus Reference Laboratory; complement-fixation tests for influenza A and B, Q fever, and the psittacosis-L.G.V. (lymphogranuloma venereum) group were negative, and there was no significant agglutination of *Streptococcus M.G.* or significant titre of cold agglutinins. W.R. and gonococcal complement-fixation tests on July 6 were negative. The erythrocyte sedimentation rate (E.S.R.) on July 4 was 114 mm. in the first hour and 120 mm. in the second hour (Westergren method). The corresponding rates on July 10, 13, 24, and August 14 were 108 and 118, 90 and 98, 15 and 38, and 8 and 18 mm., respectively. A bronchogram on August 17 showed a normal left bronchial tree. The patient was discharged on October 14. He was well apart from occasional stiffness of the ankle-joints after exercise.

Comment.—The general aspect of the patient—cyanotic, dyspnoeic, and anxious, coupled with the arthritis—suggested bronchial carcinoma with mediastinal compression and joint manifestations, but the course of the illness ruled this out. Woodland (1947) and others have described cases of pulmonary tuberculosis with associated arthritis, but the clinical features made this diagnosis untenable, and investigation of the pleural fluid revealed no evidence of tuberculosis. There was no cough, sputum, pain in the side, or polymorphonuclear leucocytosis as in bacterial pneumonia. Because of the persistent crepitations at the left base an acute exacerbation of a mild bronchiectasis

was considered in spite of the absence of a suggestive previous history, but bronchography showed a normal bronchial tree. Serological investigations did not incriminate any of the virus or rickettsial groups tested. Certain fungi, especially coccidioidomycosis, may cause pulmonary lesions and arthritis; in endemic areas skin tests with specific antigen and complement-fixation tests are of diagnostic value, but they were not considered necessary in the present case. High antistreptolysin titres have been noted in rheumatic fever (Boisvert, 1940; Bunim and McEwen, 1940) and a rising titre of antistreptolysin is reported by some as of diagnostic value. Antistreptolysin titres were not ascertained in this case. The final diagnosis was acute rheumatism with rheumatic "pneumonia" and pleural effusion.

Case 2

An obese male schoolteacher aged 42 was admitted to hospital on March 1, 1951, with a diagnosis of acute rheumatism. Eight days before admission he felt "shivery" and experienced a sensation of stiffness in the shoulders, elbows, wrists, and right knee. The right knee subsequently became swollen and painful.

On admission his temperature was 98.4° F. (36.9° C.), pulse 90, and respirations 30. His blood pressure was 150/90. Examination revealed limitation of movement of the right hip and left elbow and shoulder, and reddening and tenderness over the first left metacarpo-phalangeal joint. The patient's mental state was peculiar; he prattled childishly in answer to questions, described past trifling ailments in great detail, and claimed that he was unable to sit up or move in bed. No evidence of organic disease of the nervous system could be found. Apart from the above findings, examination was essentially negative. The temperature rose to 100° F. (37.8° C.) on March 2 and remained elevated and swinging. There was profuse sweating. Blood examinations on March 2, 5, and 12 showed: W.B.C., 12,000–20,000; 90% polymorphs. Lumbar puncture on March 5 produced a clear fluid not under pressure; cells 2 per c.mm.; total protein, 26.4 mg. per 100 ml.; sugar, 65 mg. per 100 ml.

On March 8 numerous crepitations were heard over the left lower lobe and the percussion note was impaired. There was a slight productive cough, and culture of sputum yielded a moderate growth of *Staph. albus* and *Str. viridans*. A chest film on the same day was reported as showing left lower lobe consolidation. The appearances suggested that there might also be some overlying fluid, and although the physical signs indicated only consolidation, aspiration on March 12 produced half a pint (284 ml.) of straw-coloured fluid from the left thorax.

By March 21 crepitations could no longer be heard over the left lower lobe and the percussion note was resonant over the left lung, but examination revealed signs of a large right pleural effusion. Half a pint (284 ml.) of straw-coloured fluid was aspirated from the right thorax, though much more could have been removed. A chest x-ray film on March 23 showed clear lung fields and only a slight haziness in the right cardiophrenic angle.

Several therapeutic agents were administered: chloramphenicol, 500 mg. six-hourly, from March 4 to 22; penicillin, 300,000 units four-hourly, from March 8 to 13; and "sulphatriad," 1 g. four-hourly, from March 12 to 17. These drugs had no effect on the temperature, which swung between 100 and 102° F. (37.8 and 38.9° C.) and had no apparent effect on the migratory arthritis or mental upset, although these symptoms had improved somewhat by March 19. On March 22 sodium salicylate, 120 gr. (8 g.) daily, was started, and other medication discontinued. The temperature fell to normal on the 23rd and remained normal except for rises to 99° F. (37.2° C.) on March 31 and April 8, and the arthritis at once improved and soon cleared up. The mental upset speedily disappeared. The E.S.R., which was 90 mm. in the first hour and 114 mm. in the second hour on March 23, slowly fell. It was 75 and

98 mm. on March 30, 56 and 88 mm. on April 6, 60 and 80 mm. on April 13, and 15 and 45 mm. on April 27.

On April 6 a soft systolic murmur, best heard at the mitral area and at the lower left border of the sternum, was heard for the first time, and this murmur was still present on May 1. At the latter date the general condition of the patient was excellent. There was no evidence of cardiac insufficiency at any time.

The following investigations were negative: examination of the urine for blood, albumin, sugar, bile, cells, casts, and culture for organisms; blood culture on March 7, 8, and 16; W.R. and Kahn tests on March 2 and 14; culture of faeces for dysentery and typhoid groups on March 6; serological examination for typhoid, paratyphoid, and abortus on March 6 and 20; Schuffner test for *L. icterohaemorrhagiae* and *L. canicola* on March 8; sputum for tubercle bacilli on several occasions; direct examination and culture of pleural fluid for pyogenic organisms; direct examination, culture, and guinea-pig inoculation of pleural fluid for tubercle bacilli. The blood urea was within normal limits during the course of the illness. An electrocardiogram on April 27 showed no abnormality.

Comment.—As the patient had haematemesis from a duodenal ulcer in 1939 and again in 1948, and the chest x-ray film on March 8 showed a rather high left diaphragm, the underlying condition was thought to be either a left subphrenic abscess or a bronchial carcinoma with secondaries in the brain. The first diagnosis had to be abandoned when screening on March 14 showed that the diaphragmatic elevation was due merely to gas in the stomach and intestine, and the second diagnosis was disproved by the course of the illness.

Discussion

Broadly speaking, the cases of rheumatic "pneumonia" reported fall into two main clinical groups, though many cases show features of both, and the pathology appears to be the same. In the first group the lower lobes, oftener the left, are affected, the consolidation is usually extensive, and its duration, though sometimes only a week or two, may be a matter of months. In the second group the consolidation tends to be focal, multilobular, evanescent, and migratory, though if the infection is severe the lungs may become so widely involved that death results.

Cheadle (1888), Naish (1928), Muirhead and Haley (1947), and Van Wijk (1948) have described cases which belong to the first group, and most of Rabinowitz's (1926) cases seem to come into this category. Examples of the second group of cases in which the consolidation tends to be focal and multilobular have been described (Coburn, 1933; Neuburger *et al.*, 1944; Griffith *et al.*, 1946; Jensen, 1946; Mossberger, 1947; Seldin *et al.*, 1947; Levy *et al.*, 1948; Gonzalez, 1949). In severe cases death ensued with widespread pulmonary involvement, but in milder cases the lesions tended to be migratory and ephemeral. Cough with a tenacious blood-stained sputum has been noted by several authors, including Paul (1928), Muirhead and Haley (1947), and Seldin *et al.* (1947), and the latter observers found the sputum on occasion contained frank blood. Griffith *et al.* (1946) found a blood-stained sputum in the severer cases. X-ray films showed cloudy opacities which tended to disappear and reappear in the same or other situations. Similar migratory opacities have been noted in asthma (Harkavy, 1941), angioneurotic oedema (Vaughan and Hawke, 1931; Cole and Korn, 1933), periarteritis nodosa (Weir, 1939; Elkeles, 1944), and in Löfller's syndrome (Löfller, 1932). Arthritis and pulmonary manifestations without evidence of carditis have been reported by Jensen (1946) and Van Wijk (1948).

Salicylate therapy appears to have little effect on the course of rheumatic "pneumonia." Cheadle (1888) and Seldin *et al.* (1947) stated that pyrexia was unaffected by salicylates, though Naish (1928) mentioned that in cases receiving salicylates there was little rise in temperature.

Levy *et al.* (1948) found that neither salicylates nor penicillin had any effect. Some observers have considered that the pathological changes may be due to congestion as a result of heart failure, but Epstein and Greenspan (1941) did not find the characteristic, if non-specific, pathological picture in the lungs of patients dying with pulmonary congestion as a result of hypertension, coronary thrombosis, or mitral stenosis without active rheumatic infection. Gregory and Rich (1946), by injecting rabbits with foreign protein, were able to produce changes in the lung similar to those seen in "rheumatic pneumonia." They considered that an anaphylactic angitis affecting mainly the capillaries is the essential lesion in the rheumatic lung, and that all the other findings can be explained on this basis.

In interpreting the pathological changes found in the lungs in acute rheumatism observers have differed in their estimation of the part played by cardiac insufficiency, many believing that this is the principal factor. Cases of rheumatic fever showing arthritis and pulmonary manifestations without carditis are therefore of interest, though in the absence of a specific test it is then difficult to be certain of the diagnosis of rheumatic fever. The first case described here falls into this category, and, although cardiac involvement was eventually detected in the second, there was never evidence of failure. Pulmonary manifestations in rheumatic fever may be very misleading; Griffith *et al.* (1946) state that some of their cases were diagnosed as "atypical pneumonia" until cardiac involvement became apparent.

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K. Hellmann, of the M.R.C. Climatic and Working Efficiency Unit, raises an interesting physiological point in a recent issue of *Nature* (January 19, p. 113). As is well known, the sweat glands of the skin receive an innervation from the sympathetic nervous system, but, unlike other organs under sympathetic control, are not brought into action also by adrenaline but only by pilocarpine and acetylcholine; and they are inhibited by atropine. Hellmann has been studying the cholinesterase of the sweat glands in the pad of the cat's foot by a series of histochemical tests which enable him to display the distribution of enzyme activity throughout a tissue section, and to define the enzyme's specificity of action. He finds that the enzyme is present in the terminal nerve fibres, and disappears when these degenerate, and also that its specificity differs from that of the true cholinesterases hitherto found in nerve fibres, which specialize in the hydrolysis of acetylcholine. This leads him to suggest that the sympathetic cholinergic transmitter may not be acetylcholine after all, but some allied substance.