

## CALCIFICATION OF THE INTER- VERTEBRAL DISKS

BY

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The work of Schmorl and of Alajouanine and Petit-Dutailis round about 1930 drew the attention of clinicians and pathologists to the frequency of lesions of the intervertebral disks. This stimulation of interest has, as usual, brought its reward in increased knowledge. The foundation of the modern conception of these lesions is the pathological anatomy described by Schmorl. According to his description (Fig. 1) the intervertebral disk consists of:

1. The *nucleus pulposus*—central in position, firm, elastic, and of fluid consistency—the remains of the primitive notochord.

2. The *annulus fibrosus*—non-elastic and composed of several systems of fibrous strands. (a) *Concentric fibres*. (b) *Radial fibres*: attached centrally to the nucleus pulposus and cartilage plates, and peripherally passing over the rim of the vertebral body and entering the bone just beyond this, in the manner of

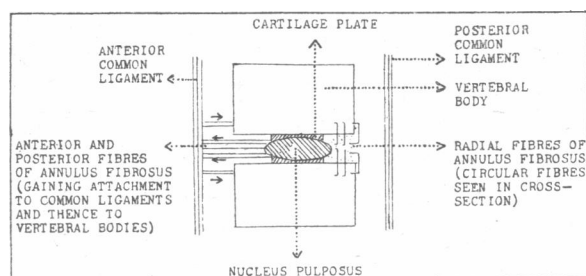


FIG. 1.—The normal intervertebral disk.

Sharpey's fibres. (c) *Anterior and posterior fibres*, similarly attached centrally, but passing backwards and forwards respectively to gain insertion into the anterior and posterior common ligaments. Fibres from these enter the vertebral bodies as Sharpey's fibres, and in this way bony attachment is secured.

3. The *cartilage plates* set on the top and bottom of the nucleus and abutting directly on the spongy bone of the vertebral body. These cartilages are the non-ossified central portions of the epiphysal plates. Through them the disk gains its nutrition by simple diffusion, and its fixation by the insertion of the fibres of the annulus.

On the basis of these anatomical considerations, certain lesions of the intervertebral disks have been described (Fig. 2).

**Nuclear Prolapse.**—Prolapse of the nucleus pulposus may occur either into the substance of the body of the vertebra or posteriorly into the spinal canal. The former is more commonly of congenital origin (perhaps there is deficiency of the cartilage plates), and it is often associated with Scheuermann's adolescent kyphosis. The retropulsed disk may be traumatic, and is associated with pressure symptoms on the spinal cord or nerve roots. Rare instances of calcification of the prolapsed portions in both types of case have been recorded by Breton, Schmorl, Cohen, and Barron.

**Anterior Annular Necrosis.**—In true senile kyphosis a necrosis of the anterior portion of the annulus fibrosus has been described (Beadle, 1931). When the bare bony surfaces of the fronts of the vertebral bodies come in contact with each other calcification (bony ankylosis) is prone to occur. The rest of the disk remains normal.

**Generalized Degeneration.**—This occurs in spondylosis deformans (Schmorl). The disks show brown degeneration or complete necrosis, and heal by granulation tissue. The instability caused by wasting of the disk leads to strain on those fibres of the annulus which are attached to the anterior and posterior common ligaments and thence to the vertebral bodies beyond the rim. Calcification of these latter fibres (i.e., the formation of osteophytes) occurs.

Anterior annular necrosis and generalized degeneration have been grouped together as spondylosis osteo-arthritica (Mercer, 1936).

**Nuclear Expansion due to Osteoporosis.**—There is loss of support of the cartilage plates by the spongy bone, and the vertebral bodies become fish-tail in shape and nuclear bulging occurs. This is typically seen in senile osteoporosis, but may occur in general rarefying bone diseases such as osteomalacia, osteitis deformans, and osteitis fibrosa cystica.

**Spondylitis Ankylopoietica (Marie-Strümpell).**—For the sake of completeness in the subsequent discussion, this malady of the

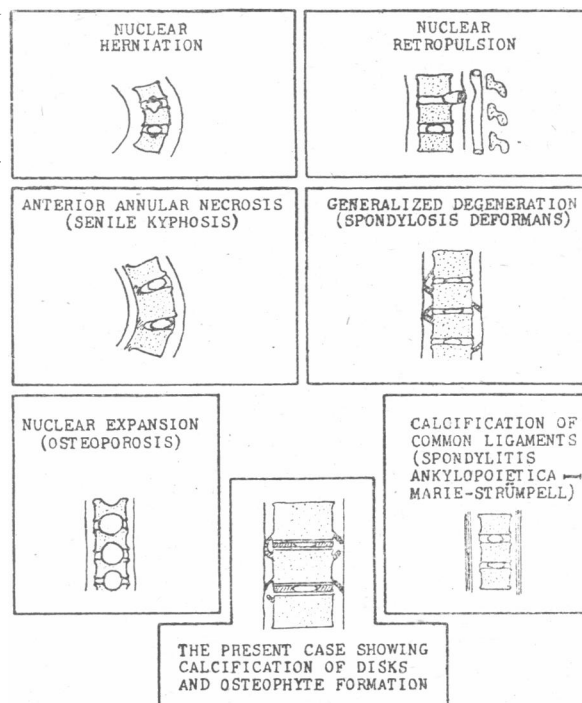


FIG. 2.—The pathological disk, showing types of calcification.

spine may be added, though strictly it does not affect the disks. Here the rigid back is due to calcification of the anterior and posterior common ligaments.

The following illustrative case recently came under my notice.

### Case Report

The patient was a man aged 49 who had sustained a gunshot wound of the left leg in France in 1917. Immediate below-knee amputation was performed. This healed satisfactorily and, wearing an artificial limb, he was able to follow his occupation of night watchman. In 1919 and 1930 the stump broke down, but responded to conservative treatment. Recently he did a lot of walking at his new job in a munitions factory, and caused an abrasion of the stump. A day or two later the stump became painful and swollen, and he had to give up work.

This man has had kidney trouble for many years. Albuminuria was noted in 1930, but was not further investigated. For some time past he has had painless nocturnal frequency, having to get up once or twice at night, and there was a yellow urethral discharge for one week in 1918. He has a stiff back, which aches, also limitation and pain on movement of shoulders, hips, and knees. There is no history of injury to the back.

On examination he was seen to be a thin, muscular man, edentulous, and did not look very ill. His skin was dry and furred. The temperature was 99°, the pulse 84, and the respirations 20. The heart showed no enlargement and there were no murmurs. The B.P. was 130/80 and the vessels were normal. There was a slightly diminished air entry at the bases of the lungs. The percussion note and vocal fremitus were normal. No adventitious sounds were heard. The abdomen was also normal.

Examination of the central nervous system showed: pupils equal, circular, reacting to light and accommodation; fundi normal; other cranial nerves normal; muscle tone and power normal, no sensory changes; biceps, triceps, knee and right ankle-jerks present; plantar response flexor.

The spine was rigid, with loss of the normal antero-posterior curves. Movement of upper cervical region was normal. Some tenderness was felt over spines of 4th and 5th lumbar vertebrae, and there was slight scoliosis with convexity to right. Shoulders, hips, and knees had movements at all joints restricted, with marked crepitus.

The 6-in. below-knee stump of the left lower extremity showed a posterior scar. The end of the stump was oedematous, and there was marked tenderness along the scar.

On Sept. 17, 1941, the prostate was enlarged, hard, and tender, and on Oct. 6 was definitely smaller, still hard, but without tenderness.

### Pathological Investigation

**Renal Tract.**—Urine (17/9/41): Sp. gr. 1020; acid; glucose nil; protein 2.8 g./litre. Microscopically, a large number of pus cells, a few R.B.C.s, and some diplococci were seen; and on culture a few colonies of staphylococci. Gram smear (25/9/41): "Threads" in urine; pus cells numerous; a few Gram-positive diplococci, no gonococci. Ziehl-Neelsen smear: No T.B. seen (6 occasions). Protein 0.3 g./litre (6/10/41). Blood N.P.N.: 17/9/41, 356 mg. per 100 c.cm.; 20/9/41, 140 mg.; 29/9/41, 76 mg.; 6/10/41, 55 mg. Urea-concentration test (Maclean): 18/9/41, 0.7%; 6/10/41, 2.7%. Radiograph of pelvis revealed presence of large prostatic calculi. Intravenous pyelogram (2/10/41): Subnormal function of both kidneys, no anatomical abnormality of pelvis, ureter, or bladder. Residual urine (2/10/41) = 1 oz.; No. 10 rubber catheter passed easily. Prostatic massage produced no discharge from urethra. Blood gonococcal complement-fixation test negative.

**Skeletal System.**—Lumbar, dorsal, and cervical spine (see Figs. 3 and 4): (1) Osteophytic outgrowths above and below

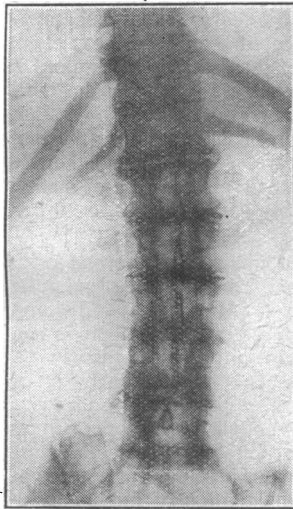


FIG. 3

FIG. 3.—Radiograph showing A.P. view of lumbar spine. Note the partial absorption of all vertebral disks, the calcification of these disks, osteophyte formation, and scoliosis.



FIG. 4

FIG. 4.—Lateral view of lumbar spine. Note partial absorption of disks, calcification apparently confined to the annulus fibres, and osteophyte formation.

the rims of the vertebral bodies. (2) Diminution of the intervertebral spaces with partial absorption of the disks. (3) Calcification of all the lumbar, dorsal, and the lower cervical intervertebral disks. Close observation suggests that this has occurred in the annulus fibrosus only, for small non-opaque areas are present in the region of the central nucleus pulposus. These changes in the disks can be seen in the lumbar spine in radiographs taken in 1930, but were not then reported—only the osteophytic growths received attention. (4) Loss of the normal antero-posterior dorso-lumbar curves, with slight scoliosis. (5) No evidence of bone disease in the vertebral bodies or of calcification of the anterior or posterior common ligaments. **Sacral area:** Sacralization of right fifth lumbar transverse process; failure of fusion of alae of 1st and 2nd sacral vertebrae. **Other joints:** Shoulders, hips, knees, and sacro-iliac joints show chronic osteo-arthritis changes. No evidence of calcification in skull, chest, abdomen, or semilunar cartilages of knees. Prostatic calculi were present. There was a spur on the posterior aspect of the stump of the tibia and a small spur on the stump of the fibula.

**General Investigations.**—A blood count showed: R.B.C., 5,040,000; Hb, 93%; C.I., 0.9; W.B.C., 12,000—polymorphs 80%, large mononuclears 2%, lymphocytes 17%, eosinophils 1%. On Sept. 20 the serum calcium was 8.2 mg. and the serum phosphorus 3.1 mg. per 100 c.cm.: both these values are low. The blood Wassermann reaction and the gonococcus complement-fixation test were negative.

### Discussion

There are many features of interest in the case described above. I think we may conclude that, as regards the genito-urinary symptoms, infection of the amputation stump produced a flare-up of the chronic calculous prostatitis, with oedematous enlargement of the gland. This led to urinary obstruction and nitrogen retention, which tended to recover as the oedema subsided. The original prostatic infection may have been gonococcal, though no actual proof of this was obtainable.

The orthopaedic changes may be summarized as follows: (1) Generalized osteo-arthritis changes are seen in all the large joints. (2) There are osteophytic outgrowths of the vertebral bodies and narrowing of the intervertebral spaces. (3) There is calcification apparently confined to the annulus fibrosus, and present in practically the whole spine, except the upper cervical region. (4) Evidence of focal sepsis (amputation stump and prostate). (5) No evidence of calcification in the anterior and posterior common ligaments of the spine, or ectopically at any other site. (6) Definite congenital abnormalities in the lumbosacral region. (7) Low blood serum calcium. (8) The changes in the spine had begun at least as early as 1930. Schmorl's differentiation of "spondylosis deformans" from other conditions formerly classified as "spondylitis deformans" is of great importance: (a) it recognizes that the pathological changes affect the intervertebral disks and bodies of the vertebrae, and accurately describes these changes; (b) it recognizes that there is not necessarily any evidence of inflammation; (c) a clear distinction is made from the "ankylopoietica" group (Marie-Strümpell), in which infection is common and the ligaments of the spine are chiefly affected. He also attempted to discard the term "osteoarthritis" for this condition of the spine on the grounds that the intervertebral disk systems do not constitute joints in the true sense of the word. The disadvantages of this point of view are well seen in the present case. For what else do we see here but a very widespread osteo-arthritis of the large joints also affecting the spine—an osteo-arthritis with marked degeneration of the intervertebral disks coupled with proliferative marginal osteophyte formation? This latter process has taken place at the points where abnormal strains are acting—viz., in the fibres attaching the annulus fibrosus to the longitudinal spinal ligaments. And these are just the changes described by Schmorl as "spondylosis deformans."

But the process has gone further still, for the fibres of the annulus fibrosus have become calcified. Now, according to the theory of Leriche and Policard, for calcification to occur there must be present three factors: an ossifiable medium; a rich source of calcium locally, and a poor blood supply (so that the calcium is not washed away). These prerequisites appear to be fulfilled here: the degenerated fibres of the annulus constitute an ossifiable medium; the vertebral bodies are a rich source of calcium; and the blood "tide"—by diffusion from the neighbouring bone—is poor. In these circumstances the likely mechanisms by which calcium salt precipitation may be determined are, first, lipid breakdown in the degenerating disk tissue followed by the formation of calcium soaps and later calcium phosphates and carbonates; or, secondly, metaplasia of connective-tissue cells to become osteoblasts which secrete phosphatase and lay down a deposit of calcium phosphate.

The suggestion that focal sepsis may have played an important part in the production of the joint condition cannot easily be denied in this case. There is indeed a source of toxic absorption (chronic calculous prostatitis) which may have been gonococcal in origin. But more accurate aetiological proof is difficult, both because the focus is hard to eradicate, and because, even if this were done, improvement in the clinical signs is scarcely to be expected at this late stage.

With regard to the congenital abnormalities in the lumbosacral region, these are commonly observed in radiographs of the spine, and are often symptomless. Also, the pathological

changes in this case have been progressive. On these grounds I think we should accept them as being of independent origin.

The low value for serum calcium is probably to be regarded as a normal finding in uraemia: it will be remembered that tetany due to hypocalcaemia is one of the causes of convulsive phenomena in this condition. Hence there is no real justification for postulating endocrine disorder (e.g., parathyroid deficiency) to explain the calcium deposit in the intervertebral disks.

### Summary

A case is described of generalized calcification of the intervertebral disks.

This condition is diagnosed as the final phase of Schmorl's "spondylosis deformans"—itself considered to be a true osteoarthritis of the spine.

An attempt is made to evaluate other factors in a complex clinico-pathological picture.

I wish to thank Dr. J. H. Mather for the radiological reports, and Prof. T. P. McMurray and Mr. W. A. Thompson for a most valuable discussion of the case, publication of which is made possible by kind permission of the Director-General of Medical Services, Ministry of Pensions.

### BIBLIOGRAPHY

- Alajouanine, T., and Petit-Dutaillis, D. (1930). *Presse méd.*, **38**, 1657.  
 Barron, M. (1926). *Arch. Path. lab. Med.*, **2**, 659.  
 Beadle, O. A. (1931). *Med. Res. Cncl. Sp. Rep. Ser.*, No. 161.  
 Brailsford, J. F. (1935). *Radiology of Bones and Joints*, p. 318, London.  
 Breton, M. (1929). *J. Radiol. Electrol.*, **13**, 277.  
 Cohen, I. (1940). *J. Mt. Sinai Hosp., N.Y.*, **6**, 255.  
 Mercer, W. (1936). *Orthopaedic Surgery*, p. 628, London.  
 Schmorl, G. (1928). *Fortschr. Röntgenstr.*, **38**, 265.  
 — (1929). *Ibid.*, **40**, 629.  
 — (1930). *Ibid.*, **41**, 359.  
 — (1931a). *Ibid.*, **43**, 202.  
 — (1931b). *Ibid.*, **44**, 1.  
 Shanks, S. C., et al. (1939). *X-Ray Diagnosis*, pp. 111, 498, London.

## SUBLINGUAL ADMINISTRATION OF METHYL TESTOSTERONE

BY

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The discovery of a preparation of testosterone that has a high degree of activity when given by mouth constitutes an advance in the treatment of those conditions for which male sex hormone therapy is indicated. Testosterone and testosterone propionate have little activity when given orally, and recourse therefore has been had to frequent intramuscular injections, periodic implantation of pellets, or the laborious daily inunction of these substances. Miescher and Tschopp (1938) first demonstrated that in castrated rats the oral administration of methyl testosterone was far more effective than that of free testosterone. Subsequent clinical observers have found that methyl testosterone by mouth produces all the effects of the injected propionate, and that to obtain equivalent results the dose required is from three to six times the dose of testosterone propionate given intramuscularly.

Sublingual therapy was first successfully applied by Anderson, Haymaker, and Henderson (1940) with desoxycorticosterone acetate in Addison's disease. The following case report shows that the effectiveness of methyl testosterone administered sublingually to a castrate is equal to, or even slightly greater than, its effectiveness when it is absorbed from the intestinal tract.

### Case Report

The patient was a man aged 23 who had been castrated in childhood because of tuberculosis in both testes. His full history and previous treatment have already been reported (Spence, 1940, Case 1). During the last 2 years, except for a control period of 4 months, during which, unknown to him, he was receiving non-medicated tablets, he has been treated with methyl testosterone by mouth. At first he was given 50 mg. a day in 5 divided doses. This dose proved to be too high, and was subsequently reduced to 5 mg. thrice daily. On this dose

normal potency was maintained. After about 4 months' treatment with methyl testosterone he married, and intercourse proved to be satisfactory. During the first 2 months of the control period, when he was receiving no active substance, intercourse was occasionally possible, but the number of his erections greatly diminished. During the second half of this period he was impotent. A dose of 10 mg. a day was not quite enough to maintain normal potency.

It was established, therefore, that the minimum swallowed dose of methyl testosterone necessary was 15 mg. a day. He was then given 5-mg. tablets of methyl testosterone (perandren linguets, Ciba Ltd.) to suck under his tongue three times a day, with instructions to avoid swallowing his saliva in order to ensure maximum sublingual absorption. The tablets disappear in 5 to 10 minutes, and are not unpleasant to taste. With this daily dose of 15 mg. sublingually, erections increased in number from "not more than 4 a week" to 6 or 7 a week, and were rather stronger than when this dose of the hormone was swallowed. A sublingual dose of 10 mg. a day produced about the same effect as 15 mg. swallowed, and therefore constitutes his maintenance dose; 30 mg. daily caused "about twice as many erections" as 10 mg. daily.

### Commentary

It should not be concluded that the maintenance dose in this patient is the same for all castrates. The dose varies in different patients, and is to be found by trial and error. Variations between 10 and 50 mg. a day are reported, but the majority of patients require a daily dose of 15 to 30 mg. when the substance is swallowed. In the treatment of eunuchism and eunuchoidism the doses of androgenic hormone during the first few months should be high—a total weekly dose of 150 to 200 mg. testosterone propionate intramuscularly—in order to bring about fairly rapid development of the secondary sexual characteristics. During this stage of treatment it would be inexpedient to rely on sublingual therapy alone, since the dose required is about 4 times the dose of the injected propionate. The most satisfactory method is to make use of intramuscular injections of the propionate or the implantation of pellets during the preliminary stages of treatment, and to reserve sublingual therapy for maintenance. In most cases the maintenance dose of methyl testosterone sublingually will probably vary from 10 to 20 mg. a day.

To explain the greater potency of methyl testosterone compared with other androgens absorbed from the intestinal tract two hypotheses have been advanced: (1) Miescher and Tschopp (1938) suggested that by virtue of the methyl group there is less destruction of methyl testosterone by intestinal ferments; (2) Biskind and Mark (1939) have shown that destruction by intestinal-ferments is unlikely, and have suggested that, as androgens are probably destroyed by the liver, methyl testosterone escapes this immediate fate after absorption possibly through its being absorbed into the lymphatic rather than into the portal vessels. In the case reported sublingual administration of methyl testosterone appears to be slightly more effective than when the substance is absorbed from the intestinal tract. It is probable that when methyl testosterone is swallowed a certain proportion of it is absorbed into the portal system and destroyed in the liver before it can exert its specific effect, whereas this danger is avoided when it is administered sublingually and absorbed direct into the systemic circulation.

### Summary

The case of a eunuch is reported in which it is shown that methyl testosterone is effective when administered sublingually. With two 5-mg. tablets a day normal potency was maintained, whereas when the substance was swallowed three 5-mg. tablets a day were required to produce the same effect.

As the sublingual dose of methyl testosterone is about 4 times the dose of testosterone propionate injected intramuscularly, and as large doses would thus be required in the early stages of the treatment of testicular deficiency, sublingual therapy should be reserved for maintenance.

I am indebted to Messrs. Ciba Ltd. for supplies of methyl testosterone (perandren linguets).

### REFERENCES

- Anderson, E., Haymaker, W., and Henderson, E. (1940). *J. Amer. med. Ass.*, **115**, 2167.  
 Biskind, G. R., and Mark, J. (1939). *Johns Hopk. Hosp. Bull.*, **65**, 212.  
 Miescher, K., and Tschopp, E. (1938). *Schweiz. med. Wschr.*, **68**, 1258.  
 Spence, A. W. (1940). *Quart. J. Med.*, n.s., **9**, 309.