VII

THE VALUE OF CALCIUM SALTS IN THE TREATMENT OF ACUTE EPIDIDYMITIS AND OTHER COMPLICATIONS OF GONORRHOEA

By A. E. W. McLACHLAN, M.B.

EPIDIDYMITIS

APART from the cardinal measures of treatment of gonococcal epididymitis, rest, support of and hot or cold applications to the affected parts, free purgation, alkaline diuretics, and cessation of urethral treatment during the acute stages, numerous therapeutic measures have been recommended to shorten the period of absolute or relative disability attending this complication. Vaccines, serotherapy, non-specific protein shock, sub-periosteal turpentine injections, intravenous injections of sulpharsphenamine, mercuric cyanide, or sodium iodide, Bier's congestion, diathermy, injection of electrargol into the epididymis, vasotomy, puncture of the epididymis, and epididymotomy have all been advocated to ensure prompt relief of the symptoms and rapid and favourable termination of the epididymitis. Many of these chemotherapeutic methods have also found application in the treatment of salpingitis and the metastatic complications of gonorrhœa.

For a number of years various salts of calcium have been employed in the treatment of acute epididymitis and other complications of gonorrhœa. Murata, in 1915, reported the successful treatment of gonorrhœal epididymitis by the intravenous injection of a calcium salt. Radnai (1922) claimed that an intravenous injection of 5 c.c. of a 10 per cent. solution of calcium chloride caused relief of the pain of a gonococcal epididymitis and prostatitis in a few hours, while two days later the patient, a soldier, carried on duty with a suspensory bandage. Ten cubic centimetres of 10 per cent. calcium chloride solution was given on the third day, and after two further doses there was complete resolution of the

BRITISH JOURNAL OF VENEREAL DISEASES

swelling. In a second case similarly treated there was an equally favourable result. Cerf (1924), after an experience of 17 cases so treated, recommended calcium chloride (10 c.c. of 10 per cent. solution at three-day intervals) as a valuable adjunct to the routine treatment to control the rapid and lasting pathological changes in gonococcal epididymitis and relieve the symptoms. Leff and Spencer (1926) came to the conclusion that the intravenous injection of 25 c.c. of 2 per cent. calcium chloride solution influenced the course of gonococcal epididymitis and rheumatism favourably, and that its use was indicated especially where pain, tenderness and swelling were present. Wade (1927) advised the intravenous injection of 15 grains of calcium chloride in the early stages of acute epididymitis. Rupel (1928) noted that in a series of 28 cases of epididymitis treated with calcium chloride intravenously there was prompt relief of pain and a lessened period of disability. He found that recurrence of the inflammation might follow too few injections, and advised a course of four or five daily injections of 0.5 to 1.0 gm. In a later publication (1934) he states: "The last 50 cases treated before calcium was considered were confined to bed for an average of 4.14 days. A total of 108 cases with calcium therapy were bed patients for an average of 2.1 days. The original report on 28 cases gave an average of 1.45 days in bed, and the 80 cases of this series gave an average of 2.37. The actual percentages show that approximately 27 per cent. got no benefit from the addition of calcium, 25 per cent. were moderately helped, and 47.5 per cent. were decidedly benefited, making a total of 72.5 per cent. which derived good from the employment of calcium in the treatment." Of the 80 cases, 48 were gonococcal and 32 non-specific; calcium gluconate was employed, at first 10 c.c. of 10 per cent. solution and later 20 per cent. solution, and by mouth. Stone (1928), in a comparison of the various treatments of acute epididymitis, recorded the relief of pain in eight hours in the only case in which calcium chloride was administered. Zau (1929) treated 58 cases of acute gonococcal epididymitis with intravenous calcium chloride: in the early cases of the series a dose of 5 to 10 c.c. of a 10 per cent. solution was employed, and in the later cases 15 to 25 c.c. of a 2 per cent. solution. The number of injections varied

TREATMENT OF ACUTE EPIDIDYMITIS

from one to five: relief of pain was noted in from two to twenty-four hours in most cases, while in twenty-seven of the patients subsidence of the swelling or diminution of the tenderness occurred on the day of the first injection. In only 1 case was there no benefit from the treatment. Iyer (1929) employed a 7.5 per cent. solution of calcium chloride with a dose of 0.5 gm. in the treatment of 16 cases of gonococcal epididymitis. He noted marked reduction of pain and swelling in less than twenty-four hours, more particularly in recent cases. Three cases failed to react. Similar favourable results were published by Ylanon (1929). McLean (1933) advised the intravenous injection of grs. x. of calcium chloride in 10 c.c. distilled water in cases of gonorrhœa with high temperature or marked discomfort. He noted no ill effects from daily repetition. The temperature dropped and the patient had a sense of well-being lasting for approximately twenty-four hours after each injection.

The chief objection raised against the use of calcium chloride is its irritant action on the tissues if injected extravascularly. Painful infiltrations, abscesses and gangrene of the skin have been observed (Seelig (1925), Zau (1929), Herrold (1930)). Nausea, vomiting, shock, and occasionally rigors coming on several hours after injection have been noted. Fishberg (1919) reported the serious collapse of a patient immediately after the injection of calcium chloride. With the exception of the late rigors, these sequelæ can be averted by careful technique and slow injection.

Other calcium salts, less irritant, and suitable for either intramuscular or intravenous injection, have been recommended as alternatives to the chloride, the gluconate (Rothlin (1927)), and the lævulinate (Greville and Dodds (1931)). Rothlin claims that despite its lower calcium content, the gluconate is physiologically equivalent to the chloride in equimolecular amounts.

Herrold (1930) treated six patients suffering from acute gonococcal epididymitis with intravenous injections of 10 c.c. 10 per cent. calcium gluconate. The average complete disability was less than two days. Five of the patients were seen within two days of the onset and the sixth at the end of two weeks. Injections were given daily for three or four days, then two or three injections on alternate days, continuing bi-weekly till the end of

BRITISH JOURNAL OF VENEREAL DISEASES

the third or fourth week. The average number of injections was 6 to 12. None of the patients suffered from recurrences. Herrold observed that if sufficient gluconate were given there was much less permanent infiltration of the epididymis. He considered therefore that this form of treatment might be of value in averting subsequent sterility in bilateral infections of the epididymis. Out of 3 cases of non-gonococcal prostatitis one patient relapsed after too early discontinuation of calcium therapy but reacted well on its resumption. Cartia (1931) treated twenty-two patients suffering from gonorrhœa or certain of its complications with calcium gluconate. He found that 4 cases of acute epididymitis improved rapidly.

ACUTE PROSTATITIS

Herrold noted relief of pain and terminal hæmaturia and decrease in the acute swelling in 4 cases of gonococcal prostatitis treated with intravenous calcium gluconate. The period of infectivity was not influenced, but the prostatic urine cleared more rapidly in the calcium treated cases than in controls, and there was less subsequent prostatic and peri-prostatic infiltration.

HYPERACUTE URETHRITIS

Herrold and Cartia observed relief of symptoms. Herrold claimed that in 2 cases gluconate therapy was of value in shortening the course of an associated inguinal adenitis and a dorsal lymphangitis, although the duration of infectivity of the gonorrhœa was not modified.

ACUTE SALPINGITIS

Vorkennel (1926), after an experience of 60 cases so treated, claimed that the cure of salpingitis could be effected in two or three days if two intravenous doses of 10 c.c. Afenil (calcium chloride and urea) were given daily. Bereskine (1927) and Botarro and Votta (1927) reported favourably of the calcium treatment of salpingitis. Zalewski (1928) advocated the combination of calcium gluconate and autohæmotherapy in the treatment of this condition: 10 c.c. of blood is withdrawn into a syringe containing 10 c.c. 10 per cent. calcium gluconate solution and mixed. One half of this mixture

TREATMENT OF ACUTE EPIDIDYMITIS

is reinjected intravenously and the other half intramuscularly into the gluteal region. Herrold (1930) treated 3 cases of acute gonococcal salpingitis with intravenous calcium gluconate injections. He found that the pain might be controlled for only twelve hours after the injection, and suggested twelve-hourly dosage for the first 48 to 72 hours. He claimed that in four patients with commencing tubal infection the exhibition of calcium gluconate controlled the symptoms and prevented further extension. Cartia (1931) observed prompt relief of pain and subsidence of the inflammation in 2 cases of acute salpingitis. These favourable results have been confirmed by Boeskin (1930), Gerwig (1930), Fekete (1931) and Diasio (1931). Pizzi (1934) showed that the calcium gluconate treatment of acute salpingitis reduced the average period of hospitalisation from 21 to 11.4 days. Pain was relieved in twenty-four hours, and the adnexal masses and pelvic exudate had undergone resolution by the end of the period of hospitalisation.

GONOCOCCAL RHEUMATISM

Leff and Spencer (1926), and Herrold (1930), claimed that the course of gonococcal rheumatism was favourably influenced by calcium salts. Gerwig (1930) reported gradual improvement and symptomatic relief in one patient in whom calcium treatment was instituted after the failure of vaccines. Cartia (1930), on the other hand, noted only relief of pain in cases of gonococcal rheumatism, calcium therapy proving of little value in shortening the course of this complication.

METHOD OF ACTION OF CALCIUM SALTS

Considerable doubt still exists as to the exact mode of action of calcium salts in controlling inflammatory processes. Wright, in 1896, attributed the effect of calcium chloride in preventing post-serum urticarias and the localised œdemas following the injection of bacterial vaccines to its action in increasing the coagulability of the blood—a view which has not been upheld by later observers. Oswald (1910) showed that the permeability of the capillary walls of inflamed areas is greatly increased. Krogh and Harrop (1920) suggested

BRITISH JOURNAL OF VENEREAL DISEASES

that this increase of permeability and the associated capillary dilatation resulted from the local accumulation of the products of tissue disintegration. Hamburger (1910) found that the action of calcium salts is to decrease capillary permeability, an observation confirmed by Chiari and Januschke (1911), Hooker (1911), Krogh (1922), and Vorkennel (1926). The result of decreased capillary permeability is to prevent the egress of cells and plasma into the inflamed area.

Blum (1921) came to the conclusion that the mode of action of calcium salts is by displacement of the sodium radical in the blood, thus preventing the availability of sodium salts necessary for the formation of inflammatory exudate. Blum showed that when following the intravenous injection of calcium salts a rabbit cornea is refractory to mustard-oil inflammation, the titre of sodium in the blood is diminished: the protective effect of calcium could be destroyed by simultaneous or subsequent injection of sodium salts.

The stimulant effect of calcium salts on phagocytosis has been studied by Hamburger and Hekma (1907), who reported increased amoeboid movements of the phagocytes, a finding confirmed by Tunnicliff (1931) and others.

Loeb (1901) demonstrated the depressant effect of calcium salts on muscular activity, while Matthews (1904) and MacCallum (1914) observed a similar reaction in regard to nerve irritability. This inhibitory action of calcium extends alike to striated and non-striated muscle and to the voluntary and autonomic nervous systems, and may in part explain the relief of pain in the complications of gonorrhœa.

Gold (1928) concluded that calcium salts inhibited the formation of experimental (pleural) exudates: the effect was, however, limited and depended largely on the dose of calcium as well as the intensity of the inflammation. Large doses of calcium were required to inhibit the effects of moderate irritation, while intense irritation was not appreciably affected by even large doses of calcium.

The action of calcium salts in the alleviation of the acute complications of gonorrhœa may be summarised:—

(1) Decrease of capillary permeability, and displacement of sodium in the blood by the calcium ions

TREATMENT OF ACUTE EPIDIDYMITIS

preventing or limiting the formation of inflammatory exudate.

- (2) Stimulation of phagocytosis.
- (3) Depression of neuro-muscular activity—causing relief of pain.
- (4) Large doses of calcium are required to achieve these effects.

PERSONAL OBSERVATIONS ON THE VALUE OF CALCIUM SALTS IN THE COMPLICATIONS OF GONORRHOEA

Observation of the value of calcium salts in the treatment of the acute complications of gonorrhœa has been made in a series of 84 cases—acute epididymitis 56, acute salpingitis 10, rheumatism 8, dorsal lymphangitis 1, suppurative inguinal adenitis 1, prostatic-vesiculitis 8. In addition, 5 cases of acute non-gonococcal epididymitis were similarly treated with calcium salts.

Various salts were employed: calcium chloride, 5 to 10 c.c. of 10 per cent solution, calcium gluconate, 5 to 10 c.c. of 10 per cent. solution, calcium lævulinate, 10 to 20 c.c. of 10 per cent. solution, calcium thiosulphate, 6 to 10 c.c. of 10 per cent. solution.* The chloride and thiosulphate can only be administered intravenously: the gluconate and lævulinate cause no untoward reaction on intramuscular or deep subcutaneous injection. All calcium salts should be injected with extreme slowness, to obviate or minimise as far as possible the transient feeling of intense heat in the skin which comes on during or immediately after intravenous injection. In several instances the intramuscular injection of the gluconate has been followed by a not unpleasant feeling of mild general flushing which persisted for several hours. Apart from one case of venous thrombosis and one instance of rigor following four hours after injection, no immediate or late sequelæ have attended this form of treatment. The number of cases treated is insufficiently large to permit of accurate assessment of the comparative value of the various salts employed.

Where possible, calcium was administered daily for

* The maximum dose of calcium thiosulphate has been increased in recent cases to 9–10 c.c. of the 10 per cent. solution in both the complications of gonorrhœa and the dermatoses following the arsenical and bismuth therapy of syphilis. No ill effects have been noticed. A dose of 12 c.c. has been repeated daily for four days without any sign of intolerance.

BRITISH JOURNAL OF VENEREAL DISEASES

three or four days, then on alternate days or twice weekly over a period of seven to fourteen days.

In the 56 cases of acute epididymitis, pain was completely relieved after the first injection in 30, after the second injection in 13, after the third or later injection in 8. Fall of the temperature to normal paralleled the relief of pain. Five patients experienced no relief, either of pain or temperature. In eight of the patients whose pain was relieved by the first injection there was recurrence of a varying degree of discomfort in from eleven to sixteen hours, relieved by subsequent injection. Resolution of the swelling commenced in twenty-four hours in 12 cases, in forty-eight hours in 16, and between the third and fifth days in 18, and was complete in eight days in 7 cases and in fifteen days in 42. In these patients the residual nodule or permanent infiltration of the affected epididymis was much less than in non-calcium treated cases. Two cases relapsed on discontinuing calcium after the third injection, but improved rapidly on its resumption.

In 5 cases of non-specific epididymitis treated with calcium salts, 4 showed rapid improvement: the fifth, after showing temporary improvement, relapsed and developed a suppurative epididymo-orchitis, necessitating operation.

Of the 10 cases of acute salpingitis, 8 showed relief of pain and drop in temperature in twenty-four to forty-eight hours, and accelerated resolution of the adnexal inflammation; one patient experienced incomplete relief of pain, and one no relief. In these two patients the course of the salpingitis was little influenced by the administration of calcium, tenderness and swelling still being present after fourteen days, as compared with an average of twelve days for complete resolution in the 8 favourable cases.

Of the 8 cases of the acute gonococcal rheumatism group 2 cases of arthralgia with early effusion into the knee joint experienced immediate relief of pain, while resorption of the effusion was complete in five and seven days respectively: two patients with tenosynovitis affecting the peroneal muscles and the extensors of the wrist respectively obtained relief of pain after the third injection, complete restoration of normal function being complete in fourteen and nineteen days. The four

TREATMENT OF ACUTE EPIDIDYMITIS

remaining patients who showed marked periarticular swelling of knee, elbow or ankle showed no beneficial reaction to the exhibition of calcium.

In 1 case of dorsal lymphangitis causing inflammatory phimosis, complicating a neglected urethritis, calcium therapy proved of no value, a dorsal slit being necessitated on the fifth day after commencing calcium injections, while in another patient an acute inguinal adenitis proceeded to suppuration despite full doses of calcium.

In 8 cases of acute prostato-vesiculitis symptomatic relief was obtained in 6: two of these patients who showed terminal hæmaturia found that this was controlled. The other two patients reported only slight alleviation of the terminal dysuria and frequency.

In several cases, not included in this series, the administration of calcium on the appearance of the premonitory symptoms of epididymitis, pain and tenderness in the groin, feeling of weight in the testis, etc., appeared to avert this complication. The dosage and course of administration were similar to that in an established case of epididymitis. Apart from these cases, the exhibition of calcium appeared to be of no value in the prevention of complications. In 5 cases in this series the calcium treatment of one complication has not prevented the incidence of a subsequent complication. Two patients developed epididymitis affecting the opposite side eight and ten days after the successful calcium treatment of a unilateral epididymitis, one patient developed a Cowper's abscess six days after cessation of calcium treatment of epididymitis; in the other two, acute arthritis occurred twelve and eighteen days after a successfully treated epididymitis.

Apart from the relief of complications, the exhibition of calcium salts has little influence on the course of a gonorrhœal infection: in this series of cases there was no appreciable shortening of the period of treatment and observation, or of the period of infectivity.

SUMMARY AND CONCLUSIONS

A review of the literature on the calcium treatment of the acute complications of gonorrhœa shows a remarkable uniformity of opinion that in certain cases, especially epididymitis and salpingitis, this measure is of value in

BRITISH JOURNAL OF VENEREAL DISEASES

the relief of pain, in the curtailment of the period of disability, and in lessening the permanent tissue damage.

In other complications, rheumatism, prostatic-vesiculitis, hyperacute urethritis, etc., relief of symptoms may be expected, with in some cases rapid improvement.

These conclusions are supported by the observation of the response to calcium therapy of a series of 84 unselected cases of the acute complications of gonorrhœa.

Calcium administration has proved of little value in shortening the normal course of gonococcal infection or in the prevention of complications.

Calcium salts, if applied therapeutically, should be administered as early as possible after the onset of the complication, in maximum doses, and over a period of seven to fourteen days.

The use of calcium salts must be regarded as an additional therapeutic measure and not as a substitute for the accepted routine methods of treatment of the acute complications of gonorrhœa.

I have to express my thanks to Mr. F. C. Endean, Director of the Department of Venereal Diseases, West London Hospital, for the clinical facilities afforded, and to Dr. David Thomson, Director of the Pickett-Thomson Research Laboratory, for access to the literature.

BIBLIOGRAPHY

- BERESKINE, M. F. (1927): *La Presse méd.*, **102**, 189.
 BLUM, L. (1921): *C. R. Soc. Biol.*, **1156**, December 18th.
 BOESKIN, F. (1930): *Zent. f. Gynäk.*, **54**, 733.
 CANTAROW, A.: "Calcium Metabolism and Calcium Therapy," Lea and Febiger.
 CARTIA, B. (1931): *Rif. Med.*, Naples, **47**, 1892, December 14th.
 CERF, A. E. (1924): *Therap. Gaz.*, **40**, 167, March 18th.
 CHIARI and JANUSCHKE (1911): *Arch. f. exp. Path. u. Pharmacol.*, **65**, 120.
 DIASIO, J. S. (1931): *Med. J. and Record*, **133**, 291.
 FEKETE (1927): *M Schr. f. Geburtsch.*, **67**, 162.
 FISHERG (1919): *J. Am. Med. Assn.*, **72**, 1881.
 GERWIG, A. (1930): *Münch. med. Wchnschr.*, **33**, 1403.
 GOLD, H. (1928): *J. Pharmacol. and Exper. Therapy*, **34**, 169;
 (1928): *Arch. Int. Med.*, **42**, 576.
 GREVILLE and DODDS (1931): *Brit. Med. J.*, August 1st.
 HAMBURGER, H. J. (1910): *Proc. Konink. Akad.*, Amsterdam, 66;
 (1922): *Biochem. Ztschr.*, **129**, 153.
 HAMBURGER and HEKMA (1907): *Biochem. Ztschr.*, **111**, 88.
 HERROLD, R. D. (1930): *Ven. Dis. Inf.*, Washington, **11**, 2, 55.
 HOOKER, D. R. (1911): *Ann. J. Physiol.*, **28**, 361.

TREATMENT OF ACUTE EPIDIDYMITIS

- IYER, S. R., (1929) : *Ind. Med. Gaz.*, 77, February.
- KROGH, A., and HARROP, G. A. (1920) : *J. Physiol.*, **54**, 125.
- LEFF, C. O., and SPENCER, O. M. (1926) : *J. Urol.*, Baltimore, **16**, 307, October.
- MACCALLUM, W. G., LAMBERT, R. A., and VOGEL, K. M. (1914) : *J. Exp. Med.*, **20**, 149.
- MCLEAN, K., (1933) : *Gen. Pract.*, 434, April 15th.
- MATTHEWS, A. P. (1904) : *Am. J. Physiol.*, **11**, 455.
- MURATA, V. (1915) : abst. *J. Am. Med. Assn.*, December 4th, 1915.
- PIZZI, F. W. (1934) : *Med. Times and Long Island Med. J.*, 348, November.
- RADNAI, E. (1922) : *Wien. klin. Wchnschr.*, **35**, 902.
- ROTHLIN, E. (1927) : *Schw. med. Woch.*, **17**, 388, April 23rd.
- RUPEL, E. (1928) : *Am. J. Med. Sc.*, **176**, 399, September ; (1934) : *Urol. and Cutan. Rev.*, **38**, 331.
- SEELIG (1925) : *J. Am. Med. Assn.*, **74**.
- STONE, E. (1928) : *J. Urol.*, Baltimore, **20**, 245.
- TUNNICLIFF, R. (1931) : *J. Infect. Dis.*, **48**, 161.
- VORKENNEL, J. (1926) : *Münch. med. Wchnschr.*, **73**, 1884.
- WADE, H. K. (1927) : *J. Urol.*, Baltimore, **18**, 427.
- WRIGHT, A. E. (1896) : *Lancet*, i., 153.
- YLANAN, C. R. (1929) : *J. Philippine Islands Med. Assn.*, **9**, 4, 128, April.
- ZAU, Z.-D. (1928) : *Nat. Med. J. China*, **14**, 368, December.
- ZALEWSKI, E. (1928) : *Med. Weld.*, **46**, 1713, November 17th.