Summary and Conclusions

A small series of patients undergoing open cardiac surgery utilizing an extracorporeal circulation was investigated to demonstrate the effect of perfusion on certain cellular components and coagulation factors of the blood.

Thrombocytopenia occurred in 12 of the 13 cases and persisted for at least 24 hours. A neutrophil leucocytosis occurred during perfusion, but the count tended to fall to previous levels by the end of the operation. There was a lymphopenia and eosinopenia.

A fall in plasma fibrinogen followed perfusion in 10 of the 13 cases, and there was increased fibrinolysis in five. A constant decrease in plasma fibrinolytic activity was present on the day after operation. The possible significance of this unexpected finding is discussed.

The use of the plasma thrombin time to demonstrate residual heparin activity after protamine neutralization is described, and this was present in six of the seven cases investigated. The other case possibly developed a circulating anticoagulant other than heparin. No tendency to bleed developed in these cases, but the investigation of coagulation factors was rendered difficult by the presence of heparin.

Changes in coagulation factors were investigated in seven cases. One-stage prothrombin times (factor V and factor VII) and serum thromboplastin generation tests (Christmas factor) were not significantly affected by perfusion even in the presence of traces of heparin. Prothrombin activity as measured by the two-stage method was more sensitive to heparin but was not grossly altered in four cases. In two other cases there was a decrease in prothrombin activity on the day after operation. Antihaemophilic globulin levels were variable, being decreased after operation in two cases and increased in three.

No correlation was found between any of the haematological changes and the duration and rate of perfusion. Excess bleeding or purpuric manifestations were not encountered in any patient.

Mr. G. H. Wooler kindly suggested this investigation and allowed access to the operation and progress notes of his patients. Mr. D. L. Greensmith rendered valuable technical assistance.

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MUMPS EPIDIDYMO-ORCHITIS AND ITS TREATMENT WITH CORTISONE

REPORT OF A CONTROLLED TRIAL

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Epididymo-orchitis occurs not uncommonly in infections with the mumps virus. Werner (1950a), in a review of the literature, quotes its incidence in mumps as between 11 and 66%, of which 18–30% were bilateral and 48–55% were followed by testicular atrophy. In his own series he noted that 4.9% of all cases of mumps, but 19% of those affected after the age of 13 years, had epididymo-orchitis, the corresponding figures for atrophy being 1.7 and 6.8% of cases of mumps. In an outbreak of mumps under circumstances similar to those forming the material for this study, Ross Russell and Donald (1958) found 48 cases of orchitis among 287 cases of Gurkha recruits with mumps. Candel (1951) noted atrophy in 5.1% and "loss of turgor" in a further 45% of 78 affected testicles seen on discharge from hospital after the attack, but in another group seen by him six years after their acute attack atrophy was present in 55% of 49 originally affected testicles; he suggested that the process of atrophy may continue after the patient becomes clinically symptom-free. Lambert (1951) concluded that testicular atrophy, as determined by quite elaborate measurements and calculations, occurred in 65.8% of cases of mumps orchitis examined by him some time after the attack.

The importance of mumps epididymo-orchitis as a cause of sterility in males is probably not great even in bilaterally affected cases (*Brit. med. J.*, 1959). Benard

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(quoted by Candel, 1951) found normal spermatozoa in adequate quantity in five cases after bilateral orchitis, though Werner (1950b) stated that 51% of 49 cases with a history of mumps epididymo-orchitis had semen "of impaired fertility"; that his criteria for normalcy were rather strict is shown by the corresponding figure of 38% in his 91 controls. Lambert (1951) also thought that a large number of those who had undergone bilateral mumps orchitis had aspermia or oligospermia.

Treatment of epididymo-orchitis has been given to relieve the acute local symptoms of swelling, pain, and tenderness as well as the pyrexia and systemic upset. Numerous reports on the use of corticosteroids in this condition have appeared, the rationale being that their anti-inflammatory action might prevent intratesticular swelling, thus relieving the local symptoms (*Lancet*, 1960) and perhaps even preventing the atrophy which may follow. Several authors—among them Solem (1954) and Bower (1956)—have described, in small personal series of cases, more or less dramatic relief of symptoms soon after starting steroid therapy, but at the same time noted the development of contralateral orchitis during treatment (Zeluff and Fatherree, 1957) and the development of orchitis in a patient whose parotitis was being treated with A.C.T.H. (Hartman, 1958). Similarly, orchitis developed during cortisone therapy in a case of mumps meningo-encephalitis (Spitznagel, 1958).

Smith and Bishir (1958), in a retrospective study of the notes of 95 patients, found that while cortisone reduced the duration of pain it did not affect the duration of swelling, fever, or stay in hospital, nor did it prevent the onset of orchitis. Petersdorf and Bennett (1957) found in 23 treated cases rapid defervescence and reduction of testicular swelling and fever, and regarded corticosteroids as the treatment of choice, though Risman (1956) found in five cases no effect on the course of ipsilateral orchitis but thought that contralateral orchitis, when it occurred, was less severe. In a series of 105 cases treated in Finnish military hospitals Klemola and Somer (1956) found no statistically significant difference in the duration of fever and orchitic symptoms in the three groups, one having placebo injections, one A.C.T.H. (daily dose 40, 20, 20, and 10 I.U., intramuscularly), and the third cortisone (daily dose 200, 200, 150, 100, 75, 50, and 25 mg. intramuscularly). They noted that in each group several cases deteriorated and several appeared to improve immediately after treatment was started. Using prednisolone 10 mg. q.i.d., Mongan (1959), in a controlled trial, treated 10 cases with a total dosage varying between 140 and 295 mg. and found that it conferred no material benefit.

Present Study

An epidemic of mumps was expected to occur in the Gurkha Depot in Malaya after the arrival of new recruits from Nepal. These came in two batches—in December, 1959, and February, 1960—and the epidemic which began in December and lasted three months affected almost 300 of them. Arrangements were made for the 35 men complaining of testicular symptoms to be admitted to hospital immediately, whether or not there had been any salivary glandular involvement. A slight difficulty arose because mumps had occurred among the second batch of recruits during their passage through and from India, so that in a few the testicular symptoms and signs were of relatively longer duration.

On admission to hospital the patients were divided into two groups by drawing out of a box for the odd—that is, first, third, etc.—case and automatically allocating the next one to the other group. All the patients were kept in bed till they felt well enough to get up, and tabs. codeine co., *N.F.*, six-hourly, were given, if required. In addition, one group received oral cortisone according to the following scheme: 75 mg. six-hourly for four doses, 50 mg. six-hourly for eight doses, 25 mg. six-hourly for eight doses, then 25 mg. 12-hourly for two doses, so that a total of 950 mg. was given over six days, beginning in each case on the day of admission.

During his stay in hospital each patient was examined every morning by one or, usually, both of us, with particular reference to testicular swelling, pain, and tenderness. The findings were charted immediately on a previously prepared form which also recorded the temperature. This was regarded as raised when 99° F. (37.2° C.) or above. No difficulty was found in deciding whether tenderness was present, and its existence was taken to indicate the continued presence of orchitis.

Serum was obtained from all the patients on the day of admission and again 10 days later. Further samples were obtained once more in all and twice in most of the patients after approximately three and six months. Complement-fixation tests using a viral-type mumps complement-fixation antigen were performed on these sera by the standard Walter Reed Army Institute for Research procedure at the U.S. Army Medical Research Unit in Kuala Lumpur. On the basis of this test Case 24, a 28-year-old instructor, was later rejected from the trial, having shown a complement-fixing antibody titre of less than 1:5 in four specimens in the absence of a history of parotitis. The other 34 cases showed one of the following: a fourfold rise of antibody (20 cases), a fourfold fall (eight cases), or a change in titre from 1:40 to 1:80 to 1:40 (six cases). Routine haematological and some biochemical studies were also carried out on these patients.

On discharge from hospital the state of the testicles was noted and all the patients were seen again, approximately three, five, and seven months later, by one or other of us, in the presence of another observer. At these follow-up examinations the state of the testicles was recorded as follows: normal, small, soft, soft and small, atrophied. At these times the observer did not know the results of the previous examinations, and this lack of bias was probably responsible for the very occasional apparently anomalous result, for it did not appear difficult to decide on the state of the testicle even when differentiating between "soft and small" and "atrophied," in the former case there being something definable to feel, in the latter virtually nothing but perhaps a slight diffuse thickening.

Results

The detailed manifestations of the illness in the untreated and treated groups are shown in Table 1. Three cases have been excluded from the appropriate calculations only where the particular data were inadequate; thus in Cases 19 and 20 the time of onset of the epididymo-orchitis was uncertain, while in Cases 20 and 25 the testicles were abnormal prior to the mumps. Case 23 is discussed in more detail below. The average day of disease in which the untreated and treated cases were admitted was 2.2 and 2.7 respectively, the range for

both groups being one to four days (excluding Cases 19 and 20). Table II shows the mean duration of the swelling, pain, tenderness, and pyrexia in each group, and these data have been worked out separately for the cases in each group admitted within 48 hours of onset. In five cases in each group the temperature was believed to have terminated by a crisis.

The state of the testicle approximately seven months after the attack in relation to the duration of the swelling, pain, tenderness, and pyrexia at the time of the acute illness is shown in Fig. 1, while Fig. 2 shows the progressive atrophic changes in the testicles in both groups over the same time.

Neither the absolute complement-fixing antibody titre nor its progressive change appeared to bear any relation to the severity of the illness or its sequelae, but there seemed to be some depression of the antibody formation in the cortisone-treated cases, as shown in Table III. This was not thought to be due to longer-than-average delay between the onset of mumps and the obtaining of the blood specimen for serology in these cases.

Liver-function tests were performed on six of the untreated and five of the treated cases. A total of 23 tests consisted of determinations of serum albumin and globulin as well as thymol and zinc sulphate turbidities. Within the limits of laboratory error it was considered

TABLE II.—Mean and Standard Deviation of the Duration of Swelling, Pain, and Tenderness in the Affected Gonads and of Pyrexia in all Patients and in Those Admitted Within 48 Hours of Onset. The Analysis of Pyrexia in the Latter Group Has Been Excluded Because of the Small Numbers, and the Fact that Four of the Nine Treated Cases were Afebrile on Admission

	All Cases			Cases Admitted Within 48 Hours of Onset		
	No. of Cases	Mean Duration Days	± S.D. Days	No. of Cases	Mean Duration Days	± S.D. Days
Swelling: Untreated ..	22	5.1	3.0	15	4.9	3.1
Treated ..	21*	4.0	2.8	10*	3.6	2.2
	0.1 < P < 0.2			0.2 < P < 0.3		
Pain: Untreated ..	22	3.0	1.7	15	3.1	1.8
Treated ..	24	2.6	1.9	11	2.6	1.7
	0.5 < P < 0.6			0.5 < P < 0.6		
Tenderness: Untreated ..	22	3.8	1.9	15	4.0	1.9
Treated ..	24	3.4	1.9	11	3.6	1.6
	0.4 < P < 0.5			0.6 < P < 0.7		
Pyrexia: Untreated ..	16	2.6	1.9			
Treated ..	18	1.1	1.1			
	0.001 < P < 0.01					

* Cases 20 and 25 excluded (see text).

TABLE I.—Clinical Features of Treated and Untreated Cases

Case No.	Age (Years)	Days Mumps before Orchitis	Days Orchitis before Admission	Side Affected	Duration after Admission—Days				Maximum Temperature °F.	State of Testicle on				
					Swelling	Pain	Tender-ness	Pyrexia		Discharge	Follow-up*			
											1	2	3	
Untreated Cases														
1	17	4	2	L	6	1	2	3	101	N	Sm	A	A	
3	18	12	1	R	0	1	4	0	—	N	N	N	N	
5	17	5	2	R	7	5	7	4	99.2	N	Sm	N	Sm	
7	18	5	3	R	9	4	5	2	103.8	Smt	N	N	N	
9†	17	8	1	R	6	2	3	3	103	Smt	Sm	A	A	
12	17	8	2	R	8	5	5	5	103.2	N	N	N	N	
14	18	?30	3	R	8	3	3	7	100	N	N	N	N	
				L	0	0	0			N	Sm	Sm	Smt	
16	18	4	2	R	8	5	7	4	104.5	N	Sm	Sm	Sm	
18	15	—	4	L	1	1	1		100	N	N	N	N	
19	18	?11	9	L	6	5	6	2	—	N	A	Sm	A	
22	14	—	2	R	5	1	2	0	102	A	A	A	A	
26	17	6	2	R	4	3	3	2	101	A	Sm	A	A	
27	17	—	3	R	7	4	5	4	101	A	A	A	A	
29	17	—	3	L	5	4	5		102	N	N	A	N	
29	14	7	2	L	6	2	3	2	102	N	N	Sm	N	
32	18	4	2	L	9	7	7	2	103	N	Smt	St	St	
32	18	4	2	R	7	3	3	1	101	N	N	N	N	
34	18	—	2	R	3	3	4	1	100	N	Sm	Sm	Sm	
				L	3	3	3			N	N	Sm	Sm	
Treated Cases														
2	17	4	2	R	5	3	3	1	102	N	Sm	A	A	
4	17	5	2	L	0	0	0	2	99.5	N	N	N	N	
6	18	3	3	R	2	2	3	3	101.4	N	Smt	Smt	Smt	
8	18	10	2	R	9	6	6	0	—	St	N	N	N	
				L	4	2	5			N	N	N	N	
10	18	8	3	R	0	0	1	0	—	N	N	N	N	
11	18	9	1	L	8	5	5	3	103	N	Sm	N	N	
13	17	8	2	L	6	1	6	1	100	N	A	Smt	A	
15	17	—	2	L	5	2	2	2	100	N	N	N	N	
17	17	—	4	R	4	4	4	2	100	N	Smt	A	A	
17	17	—	4	R	3	3	3	2	100	St	A	A	A	
20	17	?12	?	R	0	2	2	0	—					
21	17	0	2	L	6	6	6	0	—	St	Sm	A	A	
23	30	—	4	R	5	4	4	1	103	N	A	A	A	
25	19	8	1	L	5	3	3	(3)	(101)	N	Smt	Smt	Smt	
28	25	6	4	L	7	2	2	0	—	A	A	A	A	
30	14	5	4	R	3	3	4	2	101	N	N	Smt	A	
31	18	0	3	R	6	5	5	0	—	St	N	Smt	A	
33	18	12	4	L	0	0	0	1	102	N	N	St	St	
35	16	5	2	L	6	3	6	1	100	Smt	N	N	N	
				L	4	2	3	0	—	N	N	N	N	

N=Normal. Sm=Small. St=Soft. Smt=small and soft. A=Atrophied. In Case 20 a pre-existing bilateral haematocele and in Case 25 a spermatocele affected assessment of the size of the testicles.

* Follow-up examinations took place approximately three, five, and seven months after discharge.

† In addition to parotitis this patient had aseptic meningitis seven days before epididymo-orchitis.

that the total globulin was slightly raised in three patients on five occasions and that the thymol turbidity was abnormally high in five patients on six occasions, only two patients being common to both groups. The zinc sulphate turbidity was within normal limits but at the upper end of normal in five patients on six occasions. The serum alkaline phosphatase was normal in five patients on six occasions. No clinical evidence of liver disease was present in any of the cases; of the six patients who showed these slight biochemical abnormalities two were on cortisone.

Serum amylase levels were estimated in all the patients on several occasions, and the results will be presented separately.

Routine haematological studies revealed nothing of interest. The presence of eosinophilia was regarded as being due to multiple worm infestation from which these soldiers are known to suffer endemically.

Case 23.—An instructor developed right epididymo-orchitis without any preceding symptoms, and was admitted to hospital on the fourth day of his illness. He was put on cortisone, and his symptoms subsided after four days. Within 24 hours of stopping cortisone he developed contralateral orchitis, which was not treated. As the originally affected side appeared to have settled before the recurrence, it alone has been considered in the analysis of the results throughout.

TABLE III.—Effect of Cortisone on Titre of Complement-fixing Mumps Antibody

Antibody Change	Number of Cases		Total
	Untreated	Treated	
Rise $\times 4$	13	7	20
Fall $\times 4$	3	5	8
1:40 $\rightarrow$ 1:80 $\rightarrow$ 1:40 ..	0	6	6
Total	16	18	34

FIG. 1.—State of affected gonad at third follow-up (some seven months after the acute attack) in relation to duration of swelling, pain, tenderness, and pyrexia. Untreated cases shown first on each day.

Discussion

The above results show that cortisone had a statistically significant effect on the duration of the pyrexia but did not affect the duration of the other symptoms and signs, nor did it appear to have any effect on the ultimate state of the testicle. The latter appeared related to some extent to the duration of the swelling in that no cases where that had lasted for less than three days from admission (or five days from onset) showed complete atrophy seven months later.

Petersdorf and Bennett (1957) observed 23 sporadic cases over a four-year period in three different hospitals treated with three different corticosteroids in varying doses for varying lengths of time without any controls, and concluded that the hormones exerted a beneficial effect when compared with the previously described natural history of the illness. Their impression that patients who responded by crisis were less likely to show atrophic changes during the few months after acute disease and that the prompt administration of 300 mg. of cortisone or its equivalent was most important in achieving this result is not borne out by our study. Smith and Bishir (1958)—in their retrospective study of the notes of 95 cases treated over a 12-months period

FIG. 2.—Progressive changes in testicles over seven months. The three follow-up examinations took place some three, five, and seven months after the attack.

by different observers by slightly different symptomatic measures, as well as in some cases by different antibiotics in addition to cortisone or A.C.T.H. administered by different routes in varying doses for varying periods—came to the conclusion that cortisone was beneficial in diminishing pain in and swelling of the testicle, when compared with a group, not necessarily equivalent, treated symptomatically only. However, in their properly controlled trial Klemola and Somer (1956) found an absence of the effect of steroids on the symptoms of orchitis similar to that in our study, but in their cases the temperature did remain raised for a little longer. Mongan's (1959) findings were similar.

The fact that cortisone appeared to have no effect on the later history of the affected testicles which may be related to the duration of the original swelling agrees with its absence of effect on the latter. It was of interest to observe changes in testes not affected to our knowledge at any time by an acute process, and it would have been of great interest to examine the testicles of all the men in the depot on arrival and follow them up at intervals throughout the epidemic and after, whether or not they had had clinical mumps.

Abnormality of liver-function tests was mentioned by Petersdorf and Bennett (1957), and some possible disturbance was found in 6 of our 11 patients in whom it was sought. These patients were selected only in so far as they were among the last 13 patients in our series.

Finally, although no testicular biopsies or sperm counts were performed on these patients, it is hoped that they may all be followed up for some years so that further testicular changes and their effect may be observed.

Summary and Conclusion

During an epidemic of mumps in an Army depot all the 35 cases of orchitis were admitted to hospital and treated with bed rest and simple analgesics. Half, selected at random, were also given a six-day course of cortisone as described above. One case was later excluded because of the absence of serological evidence of mumps, which was present in the other 34 cases. All the patients were examined daily, and observations were charted on a previously prepared form by one of two observers. All the patients were seen again approximately three, five, and seven months later by one or other of the observers.

The following observations were made: (1) At the time of the acute illness cortisone in the dosage administered had no statistically significant effect on the duration of the swelling, the pain, or the tenderness of the affected testicle, even in cases treated within 48 hours of onset. (2) In the cortisone-treated group the duration of the pyrexia was slightly reduced from a mean of 2.6 days to one of 1.1 days; this reduction was found to be statistically significant ($P < 0.01$); the mode of termination of the pyrexia had no relation to treatment or to the sequelae. (3) Testicular degeneration, as evidenced by a loss of consistency and a decrease in size leading in some to complete atrophy, was found to be progressive for at least five months after the acute attack; it did not appear to have been influenced by previous cortisone therapy. (4) The ultimate state of the testicle some seven months after the acute attack did not appear to be related to the duration of the pain, the tenderness, or the pyrexia, but may perhaps have been influenced by the duration of the swelling at the time of the attack. (5) Cortisone appeared to depress the forma-

tion of complement-fixing antibody, but the level of the latter did not seem to be related to the symptoms, signs, or sequelae of the attack. (6) The serum globulin and thymol turbidity were slightly raised in 6 of the 11 patients in whom they were determined.

It is thought that neither the previously reported cases nor the present trial show any evidence of the efficacy of steroids in the treatment of mumps epididymo-orchitis.

We are grateful to Brigadier M. F. H. Kelleher, late R.A.M.C., for his enthusiastic support, and to Lieutenant-Colonel A. D. Young, R.A.M.C., for his encouragement throughout. The trial would have been impossible without the continuous co-operation of Drs. Frank Scott and P. J. Murphy, formerly Captains, R.A.M.C., at the Gurkha Depot, Sungei Patani, to whom we are indebted. We thank Lieutenant-Colonel Hinton J. Baker, M.C., for the virus studies performed at the U.S.A.M.R.U.; Drs. B. L. Elisberg and P. A. Webb for much stimulation; and Dr. David B. Evans, formerly Captain, R.A.M.C., for the routine investigations.

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CAUDA EQUINA LESIONS ASSOCIATED WITH ANKYLOSING SPONDYLITIS REPORT OF THREE CASES

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Ankylosing spondylitis is a not uncommon disease which has been extensively studied and described. Recent reviews of the disease include those of Baird *et al.* (1955), Hart (1955, 1959), Baird (1956), Swezey *et al.* (1957), Lefkovits and Thomas (1958), and Graham (1960). A search of the available literature has revealed no description of an association between this disorder and lesions of the cauda equina.

We have observed three patients with long-standing, quiescent spondylitis who developed cauda equina lesions many years after the active disease process had settled. Investigation revealed no cause for these defects. There is no direct evidence that the neurological abnormality is caused by the ankylosing spondylitis, but the similarity of the clinical picture in these three patients is such as to suggest that a causal relationship may well exist.