staphylococcal carriers can be effectively isolated. Four single rooms are provided on this plan, and it was suggested that these should be used for segregating carriers. However, these rooms are for the use of the seriously ill, and the nasal carriers are usually well patients who may not require operation as part of their treatment. (3) Each four-bedded unit is provided with its own toilet and basin. They also have a self-closing door and are exhaust-ventilated.

The results of this type of planning are yet to be observed. The baseline has been established over some two and a half years and the incidence of wound infection, cross-infections, and the trends in them have been recorded. The same system of observation will continue when the new block is used, and an accurate comparison should be possible. This will be of value in indicating the effectiveness of the overall planning, but, unfortunately, it will not help in elucidating the present most pressing problem—What is the comparative importance of the various measures necessary to deal effectively with staphylococcal cross-infection; which ones are major and mandatory and which are minor but desirable? Until these are known our attack is unfortunately diffuse and dispersed, and the inclination to deal with the problem by ignoring it can go largely unchallenged.

Summary

A detailed survey of wound infection in a surgical unit in Sydney strongly suggests that infection is mainly occurring in the wards. Spray-on plastic dressings have been helpful in reducing the infection rate.

Extensive colonization with staphylococci of the noses of patients and staff were observed. Weekly rates of colonization were: patients 10%, staff 6%. Nasal staphylococcal carriers showed a wound-infection rate double that of those whose noses were clear, and as a result had a higher morbidity and a longer hospital stay.

Such observations require changes in the physical planning of hospitals, and the broad principles of such a plan are suggested.

A most useful grant for work on wound infection from the Post-Graduate Committee in Medicine of the University of Sydney is gratefully acknowledged.

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"Was a hunting accident the cause of Sir Charles Hastings's choice of medicine as a career? This was the theory presented by Canon J. S. Leatherbarrow, Rector of Martley, at [a] meeting of Worcestershire Archaeological Society. In a paper on the Hastings family, who occupied the living of Martley for 150 years, and provided excellent examples of the squire-cum-parson, or 'squarson' of the nineteenth century, Mr. Leatherbarrow told members of an incident which took place when Charles was 12. His father, the Reverend James Hastings, was thrown from his horse and wandered home dazed and in a state of mind which made him a near-lunatic for 50 years. The rector entered the house and sat on the bottom of the stairs. It was Charles who succeeded in persuading him to go to bed, and it is possible that the experience either created or extended an interest in medicine that eventually made Sir Charles one of the greatest surgeons of all time." (*Berrow's Worcester Journal*, April 6.)

PLACE OF SURGERY IN EARLY STAGES OF ACUTE OSTEOMYELITIS

BY

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[WITH SPECIAL PLATE]

Sir Robert Hutchison once said, "Be not the first by whom the new is tried, nor yet the last to lay the old aside." These words are relevant, for as new and powerful antibiotics become available there may be a tendency to lose sight of the value of surgery—a long-established method of treatment.

It is certainly true that most patients with acute osteomyelitis are cured with antibiotics alone if these are given early enough—that is, in the first three days of the illness—and for a long enough time; few would disagree that drainage of the abscess (whether by open operation or aspiration) plays an important part in the treatment of many of the patients by the time they are admitted to hospital. However, there is no general agreement on the timing of drainage, or on the relative merits of aspiration and open drainage. This paper is principally concerned with these two aspects, and is based on a study of 84 unselected patients; 45 of them, seen at Fulham Hospital, London, have been reviewed elsewhere (Harris, 1960), but only brief reference was made to the place of surgery in treatment. Most of the remaining 39 patients have been seen at the Royal National Orthopaedic Hospital, and a few at other hospitals in the London area.

Detailed antibiotic therapy will not be discussed in this paper; it has played, and continues to play, a vital role in the management of acute osteomyelitis, but the relative merits of antibiotics and surgery could be decided only by a carefully controlled clinical trial, and this is ethically undesirable.

Pathological Basis for Early Surgical Drainage

Early operation is based mainly on the fact that certain important pathological changes occur in the bone during the first few days of the illness. These changes will be described briefly.

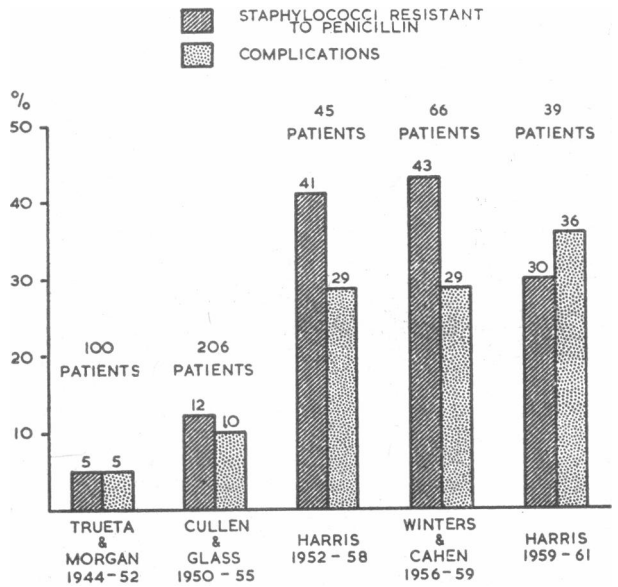
By the second or third day, in the classic acute type of illness, pus has formed, the periosteum is raised over a variable extent, and the vascular supply has become compromised; the pus is under considerable pressure, and if this is not relieved thrombosis of vessels may occur, leading inevitably to some degree of bone necrosis. Early and complete decompression of the bone before the blood-supply is interrupted will prevent or reduce this necrosis. It is unfortunate, therefore, that the story of the disease has been written (because of late diagnosis) by the time many of the patients are admitted to hospital.

Trueta and Morgan (1954), in describing these early pathological changes, made this significant statement: "Penicillin alone cannot prevent bone changes occurring after the blood-supply is interrupted; early surgery is just as necessary now as in pre-penicillin times." This advice is still relevant and applies to all antibiotics.

Causative Organism

The coagulase-positive staphylococcus is by far the most commonly isolated organism, and a high incidence of penicillin-resistant staphylococci has been reported in

several recent series (see histogram). The importance of testing the antibiotic sensitivity is evident. Culture of the blood is sterile in about 50% of cases (Harris, 1960), so the only certain method of obtaining the organism is by surgical drainage.



Histogram to show percentage of penicillin-resistant staphylococci and complications in several reported series.

A further disadvantage of relying on blood culture is that it takes at least 24 hours longer to obtain a result than when a specimen of pus is cultured; a sensitivity report on the pus can be provided on the day following operation.

From the 84 cases 64 organisms were isolated, and 35% of these were resistant to penicillin.

Complications

Incidence

A complication is defined as a chronic infection with a discharging sinus or obvious sequestrum formation. The number of complications (see histogram) remains disturbingly high, and this in spite of the many antibiotics available. In 1944, at the beginning of Trueta and Morgan's series, penicillin was becoming generally available, and these authors' figures make an interesting comparison with the later series. It is not without significance that the incidence of complications has risen steeply in the last ten years, and during this time the percentage of penicillin-resistant staphylococci has also increased.

These facts are of practical importance, because penicillin remains the most commonly used drug in treating osteomyelitis, though nowadays it is usually combined with a second antibiotic.

The incidence of complications in the series was 31%.

Causes

It is probable that the increasing number of complications is in part due to treating patients with penicillin when subsequent isolation of the organism shows it to be resistant to the drug; delay in starting effective antibiotic therapy occurred in 11 cases out of 27 with complications. Early drainage to obtain the organism will overcome this difficulty.

There are other causes of complications which are influenced by early surgery, and they fall into two groups:

(1) *Incorrect Diagnosis.*—This will inevitably delay effective antibiotic therapy; however, surgical drainage will confirm the diagnosis, and no harm will result if it is wrong, but one may often regret not operating.

(2) *Surgical Errors.*—In this series the errors were of two types: first, a deliberate policy to avoid operation until the clinical response to antibiotics has been noted; and, secondly, inadequate drainage. These two errors will now be discussed.

For reasons given earlier, severe bone changes are likely to develop if surgery is delayed; therefore the policy referred to is probably a dangerous one, unless, of course, antibiotic therapy has been started during the first three days of the illness. In this series a combination of early antibiotic therapy and early surgery gave the best results (Table I), but the number of patients in this group is very small. However, a significant number of complications occurred when surgery and antibiotic therapy were late; the number was smaller with late surgery and early antibiotic treatment.

TABLE I.—*Analysis of 52 Operations (Open, 40; Aspirations, 12)*

Operation (Days After Onset of Illness)	No. of Patients	Antibiotic Therapy (Days After Onset of Illness)			
		Early (1–3 Days)		Late (Over 3 Days)	
		No. of Patients	Complications	No. of Patients	Complications
Early (1–3) ..	7	5	0	2	1
Late (over 3) ..	45	19	3	26	11
Total ..	52	24	3	28	12

There are two aspects to the problem of inadequate drainage. The first is whether the bone should be drilled, or whether it is enough simply to drain the subperiosteal pus. In order to ensure adequate decompression the bone should be drilled; this view is based on the early pathology of the lesion and the findings at operation. The drainage of subperiosteal pus does not necessarily decompress the bone, for when the latter is drilled the pus is often found to be still under tension. The second aspect to consider is whether open drainage is to be preferred to aspiration. Twelve patients in the series were treated by aspiration; four complications occurred in this small group, in patients who had late antibiotic treatment and late aspiration (Table II).

TABLE II.—*Analysis of 12 Aspirations*

Aspiration (Days After Onset of Illness)	No. of Patients	Antibiotic Therapy (Days After Onset of Illness)			
		Early (1–3 Days)		Late (Over 3 Days)	
		No. of Patients	Complications	No. of Patients	Com plications
Early (1–3) ..	2	1	0	1	0
Late (over 3) ..	10	1	0	9	4
Total ..	12	2	0	10	4

Bremner *et al.* (1954) carried out a controlled trial of open drainage and aspiration in a small series of selected patients. They found no significant difference in the results of the two groups, but stressed some of the disadvantages of aspiration. Experience with the method confirms that the disadvantages are: (1) full decompression of the bone is not always possible: even when the pus is located (and this may be difficult) it may not pass along the widest-bore needle; (2) frequent daily assessment is necessary; and (3) repeated aspiration is usually required, and this is undesirable.

The Place of Aspiration

Aspiration has a part to play in the management of acute bone infections, and is the method of choice in treating septic arthritis; it is also of value in spinal disease, because the abscess not uncommonly presents superficially, and it can then be aspirated without difficulty, the purpose being to obtain the organism and not to decompress. Osteomyelitis of the spine appears to be a different disease from that which occurs in the long bones, and the prognosis is excellent in most patients when antibiotics alone are used; other workers subscribe to these findings (Pritchard and Thompson, 1960; Garcia and Grantham, 1960). A good result will be obtained even if treatment is started many weeks after the onset. There are 10 patients with spinal infection in the series. Of these, two relapsed because the course of drug therapy was too short; the remaining eight patients began treatment between 12 days and 11 months after the onset of their illness, and they have all done well. Only one had an operation, six months after the illness started, because it was thought to be tuberculosis.

Patients with Complications

Short case histories of some of the patients who developed complications will now be presented, and these, with their radiographs, will serve to illustrate the points that have been referred to earlier.

Case 1

A girl aged 13 was admitted 26 days after the onset of the disease. Special Plate, Fig. 1, shows that severe bone changes had already occurred, and therefore open drainage performed the next day could not influence the subsequent events; however, it resulted in isolation of the staphylococcus, which was found to be resistant to penicillin. She was given a course of tetracycline and erythromycin for six months. A radical removal of dead bone was carried out five months after onset (Special Plate, Fig. 2). She then made an uninterrupted recovery, and remains symptom-free 18 months from onset (Special Plate, Fig. 3).

COMMENT.—Serious bone changes, as in this patient, should not be seen provided treatment, which may include open drainage, is early and efficient. This case also illustrates the value of a radical operation in late disease.

Case 2

A man aged 32 with infection of the tenth and eleventh thoracic vertebrae (Special Plate, Fig. 4) was admitted under the care of the physicians seven days after the onset of his illness, when a diagnosis of meningitis was made. Blood culture produced a penicillin-resistant staphylococcus, and a large loin abscess was aspirated seven weeks after the onset; the first signs of paraplegia were noted at this time. Tetracycline administration was started empirically 12 days after onset, and subsequently he had a course of novobiocin with erythromycin, antibiotics being given for a total of seven months. Recovery was complete, and he remained symptom-free 18 months after onset, there being no residual neurological signs (Special Plate, Figs. 5 and 6).

COMMENT.—This case illustrates the good prognosis in osteomyelitis of the spine despite late treatment. Complete decompression of the bone was not necessary.

Case 3

A boy aged 13 was admitted under the care of the physicians three days after the onset. The signs were confined to the right hip (Special Plate, Fig. 7), but a diagnosis of rheumatism was made and he was treated with aspirin and penicillin. Aspiration was not performed, and open drainage of the joint was delayed until 17 days after onset. Blood culture produced a penicillin-resistant staphylococcus, and treatment was continued with tetracycline and erythromycin.

COMMENT.—Despite the relatively early treatment with antibiotics, serious complications developed (Special Plate, Fig. 8). This catastrophe would probably have been avoided if the joint had been aspirated on admission.

Case 4

A boy aged 7 was admitted to hospital seven days after onset. Treatment consisted of three aspirations, also penicillin injections for a month, despite the presence of a staphylococcus resistant to the drug. Severe bone changes were already present at the time of his discharge (Special Plate, Fig. 9A). A chronic bone infection became firmly established (Special Plate, Fig. 9B), and a persistently discharging sinus developed.

COMMENT. — This tragedy occurred because of inadequate drainage and inefficient antibiotic therapy. Radical surgery, as in Case 1, is probably the treatment of choice, and this will be undertaken at the appropriate time.

Case 5

A girl aged 12 was admitted three days after onset. She was treated at first with penicillin and aspirin, a diagnosis of acute rheumatism having been made; blood culture was sterile. The initial good response to treatment was not maintained, and 19 days after onset extensive bone changes were present (Special Plate, Fig. 10A); a sequestrum was clearly visible some three weeks later (Special Plate, Fig. 10B). The course of antibiotic therapy lasted seven months, and, though she remains symptom-free one year after onset, the bone has never completely healed (Special Plate, Fig. 10C).

COMMENT. — Despite early antibiotic therapy, sequestrum formation was not prevented. The prolonged course of drugs has not cured the bone lesion. It seems likely that drainage on admission would have prevented the bone changes and avoided the need for prolonged antibiotic treatment. It is likely that surgery will be required at some time to allow complete healing to occur.

LEGENDS TO SPECIAL PLATE : N. H. HARRIS

FIG. 1.—Case 1. Radiograph taken on admission, 26 days after onset. Note severe bone changes; no treatment given before admission.

FIG. 2.—Case 1. Appearance on day of operation, five months after onset, radical excision of dead bone having been performed.

FIG. 3.—Case 1. Fourteen months after onset. Note improved bone texture.

FIG. 4.—Case 2. Radiograph taken 11 days after onset. Note narrowed disk space between 10th and 11th thoracic vertebrae, and a paravertebral abscess (arrows).

FIGS. 5 and 6.—Case 2. Radiographs taken 14 months after onset. Note that healing is advanced and fusion is taking place between the two affected vertebrae.

FIG. 7.—Case 3. Radiograph taken 13 days after onset of septic arthritis of right hip. Note narrow joint space.

FIG. 8.—Case 3. Three months later, showing destroyed hip.

FIG. 9.—Case 4. A. Radiograph taken one month after onset; extensive bone changes present. B. Five months later (six months after onset). There is a large abscess cavity containing a sequestrum; typical changes of well-established chronic bone infection are seen.

FIG. 10.—Case 5. A. Radiograph taken 19 days after onset. Note extensive bone changes; penicillin had been given for 16 days. B. Twenty-four days later; a large sequestrum is visible. C. One year after onset; healing has not yet occurred.

FIG. 11.—Case 6. A. Radiograph taken 17 days after onset; drill holes are visible and a minimal periosteal reaction is present. B. One month later; severe bone destruction has occurred.

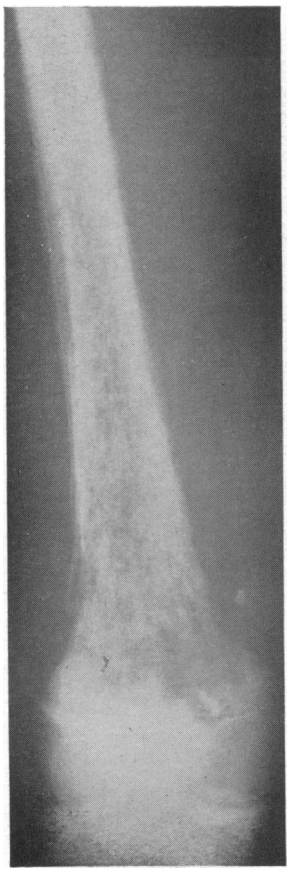
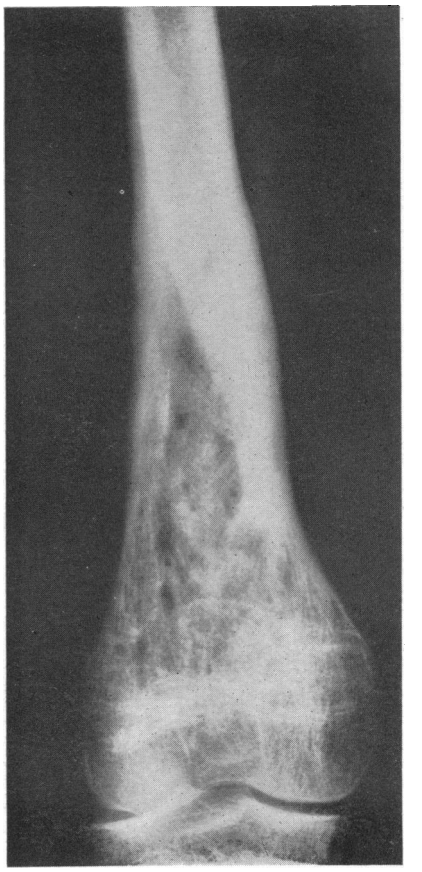


FIG. 1

FIG. 2



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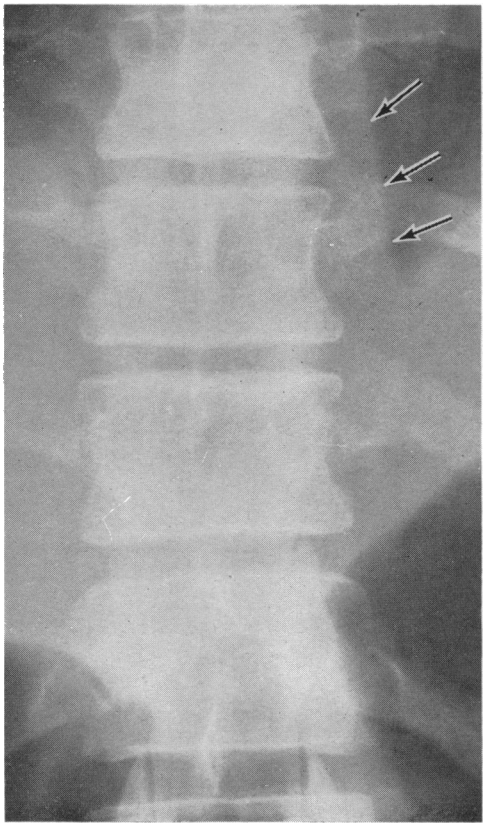

FIG. 4

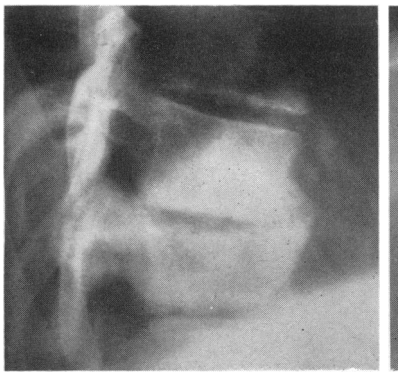

FIG. 5

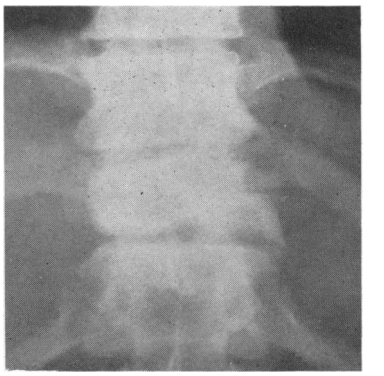

FIG. 6

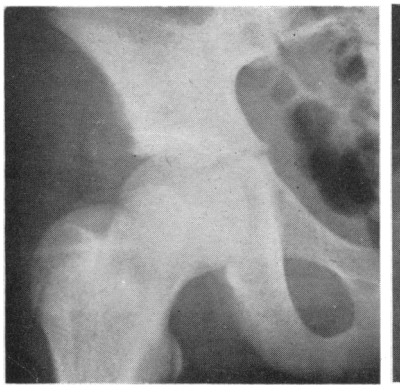

FIG. 7

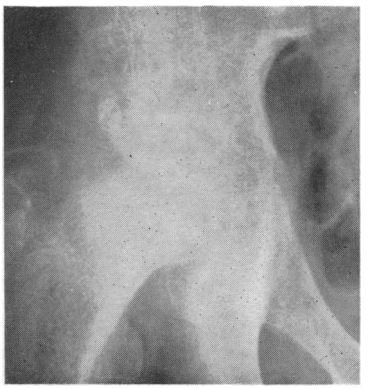

FIG. 8

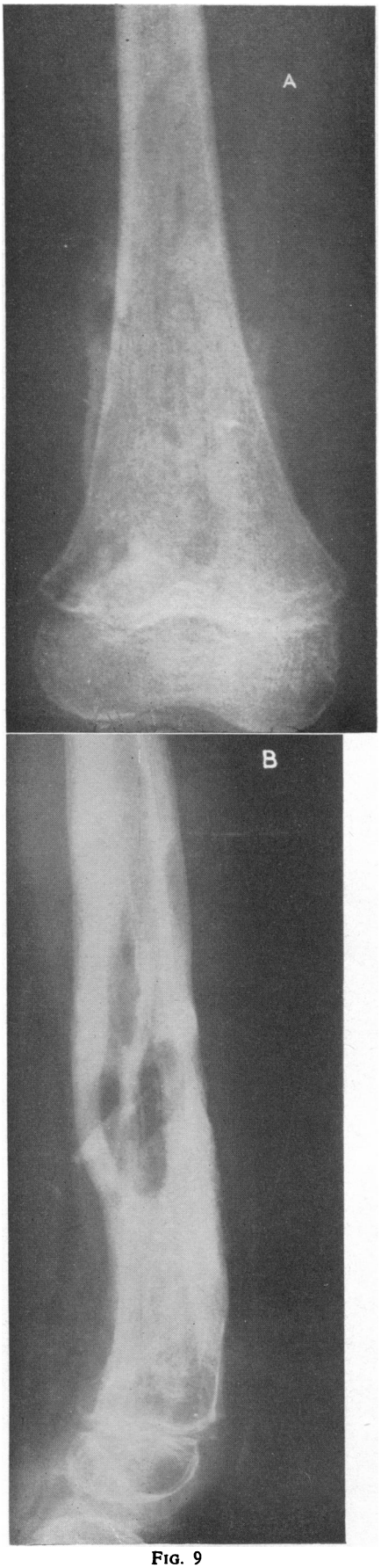

FIG. 9

FIG. 10

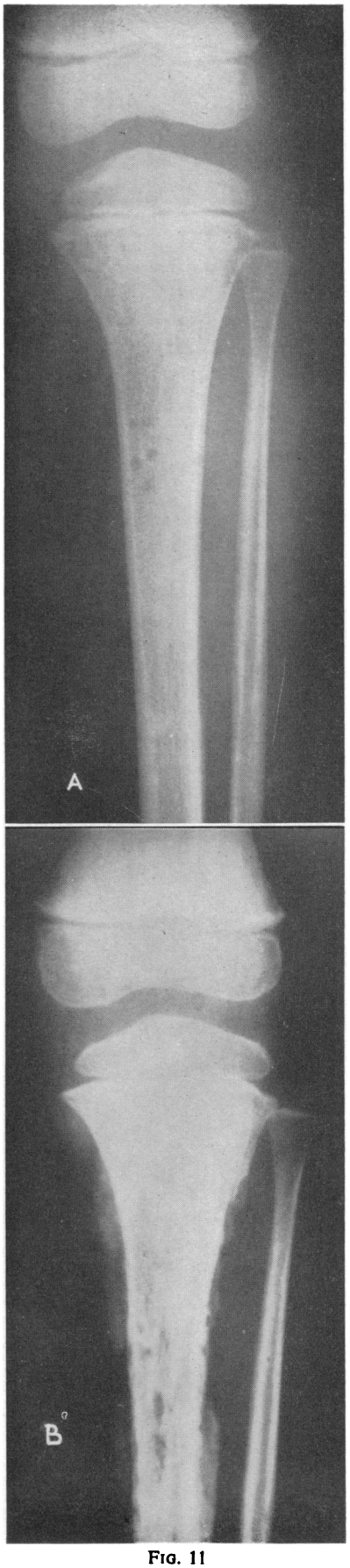

FIG. 11

Case 6

A boy aged 7 was admitted three days after onset and penicillin injections were started at once. He did not improve because the staphylococcus isolated from the blood was resistant to the drug. Three days later (six days after onset) the penicillin was replaced by chloramphenicol and erythromycin, and the next day open drainage was performed. The earliest bone changes were seen on the radiograph taken ten days after operation (Special Plate, Fig. 11A). A persistent sinus developed, and a subsequent radiograph showed that extensive bone destruction had occurred (Special Plate, Fig. 11B).

COMMENT.—This patient was admitted in the early stages of the illness, but decompression was delayed until the effects of antibiotic therapy had been observed ; this policy led to the development of a severe chronic bone infection. If he had been operated on when he was admitted it is likely that only minimal bone changes would have developed. The antibiotic treatment could not have had much effect during the vital early days of the illness, because the staphylococcus was resistant to penicillin. Isolation of the organism at operation would have made possible a report on its antibiotic sensitivity the next day, thus permitting effective antibiotic therapy to be started four, instead of six, days after the onset.

Conclusions

The complications of acute osteomyelitis are preventable, and the present high incidence could be reduced appreciably if the policy of early surgical drainage were to be more widely adopted. Such a policy may be stated quite simply.

If the illness has lasted 48 hours or more when the patient is admitted, drain the same day ; if less than 48 hours, drain if there is no clinical improvement after 24 hours' antibiotic therapy, especially if the sensitivity of the organism is not known. If there is any doubt as to the date of onset it is best to drain. Unless the diagnosis is made earlier than it is at present this policy will mean that almost all patients will have an operation ; it will also mean that some unnecessary operations will be performed, because the virulence of the organism and the patient's resistance are variable, but this seems a small price to pay if the disaster of chronic bone infection can be prevented.

Surgery is to be preferred to aspiration, and the bone should be drilled even if subperiosteal pus is present. There are two exceptions to open drainage: (1) primary joint infections, when early aspiration is the method of choice ; and (2) infections of the spine, which are cured with antibiotics alone in most cases, though aspiration of an accessible abscess is a useful ancillary procedure.

The advantages of early drainage are: (1) the diagnosis is confirmed and the organism is obtained for sensitivity tests ; (2) vascular damage and bone necrosis are prevented or reduced to a minimum ; (3) relief of pain is dramatic after operation ; (4) it is a simple procedure, not requiring specialized surgical training, and this is an important consideration in countries where the disease is common and strict medical supervision is not always possible.

It is clear that acute osteomyelitis remains a surgical disease, even though most of the patients treated with antibiotics in the first three days are cured and surgery is avoided. On the evidence presented, these patients should be admitted to an orthopaedic ward if possible, and the physicians and paediatricians ought to be encouraged to seek a surgical opinion on their patients as soon as they are admitted ; after all, appendicitis is often treated conservatively, but always in a surgical ward.

Sir Harry Platt (1928) summarized the position in regard to surgical treatment in the pre-antibiotic era when he stated: "A small incision down to the metaphysis at the point of maximum tenderness and puncture of the bone by a series of small drill holes will save many limbs and many lives." The availability of antibiotics has not altered this view, and in advising on treatment to-day he might well say that a course of antibiotics saves life and may save the limb ; but combine antibiotics with early surgery, then life and limb may both be saved.

Summary

The place of surgery in acute osteomyelitis is discussed on the basis of a study of 84 cases. The pathological basis for early decompression of the bone is outlined. Of the staphylococci isolated, 35% were resistant to penicillin.

The causes of complications, which developed in 31% of the patients, are discussed, and the place of early surgery in their prevention is indicated. Among the advantages of early surgical drainage are the isolation of the organism for sensitivity tests, confirming the diagnosis, and prevention of vascular damage. Open drainage with drilling of the bone is preferable to aspiration, and the disadvantages of the latter are discussed. Aspiration has a place in treatment, and is the method of choice in septic arthritis and spinal infection. It is suggested that osteomyelitis of the spine has a different natural history from that of the long bones ; the good results from conservative treatment are consistent with this view. Case histories of patients who developed complications are given as examples of the problems discussed.

Acute osteomyelitis is a surgical disease, and patients should be admitted to a surgical ward for treatment. If the illness has lasted 48 hours or more before admission, or if there has been no response to antibiotic treatment started during the first 48 hours, operation is advised, especially if the sensitivity of the organism is not known.

Part of this work involved travelling to a number of hospitals in and around London. My grateful thanks are due to the Joint Clinical Research Committee of the Royal National Orthopaedic Hospital and the Institute of Orthopaedics, London, who provided a grant for this purpose ;

LEGENDS TO SPECIAL PLATE : W. J. IRVINE

FIG. 1.—Morphology of "microsomal" fraction prepared as shown in Text Fig. 6. (Electron-micrograph. ×16,000.)

FIG. 2.—Epithelial-like cells spreading out from explant of simple goitre after four days in plasma clot containing 25% "standard" cytotoxic serum. (Inverted phase contrast. ×184.)

FIG. 3.—Cells from periphery of same culture as Fig. 2 after eight days *in vitro*, demonstrating their epithelioid nature. (Inverted phase contrast. ×280.)

FIG. 4.—Periphery of explant of a Hashimoto gland after two days' culture in plasma clot containing 25% "standard" cytotoxic serum. (Inverted phase contrast. ×338.)

FIG. 5.—Same explant as Fig. 4, but after six days' culture in presence of 25% cytotoxic serum. Note presence of fusiform cells as well as round cells; fusiform cells could be derived either from glandular epithelium or from fibroblasts. (Inverted phase contrast. ×300.)

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STUDIES ON THE CYTOTOXIC FACTOR IN THYROID DISEASE

BY

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[WITH SPECIAL PLATE]

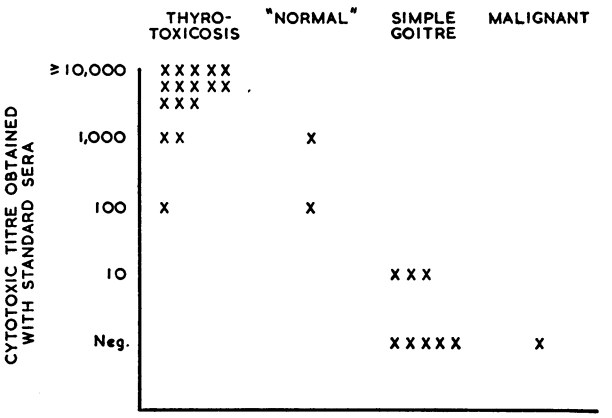
Cells derived from human pathological thyroid glands may be readily cultured *in vitro* as monolayers (Pulvertaft, Davies, *et al.*, 1959; Irvine, 1959, 1960a). In brief, human thyroid tissue obtained at thyroidectomy is cut into fine portions, washed, and transferred to 0.25% trypsin (Difco) in balanced salt solution. With incubation at 37° C. and with intermittent shaking, clumps of cells come into suspension, and these can be separated from lymphocytes and red blood cells by very slow centrifugation. Finally the cell clumps are resuspended in nutrient medium containing a total of 20% human serum and synthetic medium "199" (Morgan *et al.*, 1950) as diluent. The fact that these clumps of trypsinized cells are derived from the thyroid epithelium and not from any other tissue within the thyroid has been established by studying their morphology under the electron microscope (Irvine and Muir, 1962).

Some of the conditions that are necessary for a serum from a patient with Hashimoto's disease to have a cytotoxic effect on human thyroid cells *in vitro* were reported by Pulvertaft, Doniach, *et al.* (1959), and many of the properties of the humoral cytotoxic factor responsible for this effect were subsequently described by Irvine (1960b, 1961a) and confirmed by Pulvertaft *et al.* (1961). The purpose of this paper is to present the results of a more extensive study of the occurrence of the cytotoxic factor and to clarify some points which were hitherto unresolved or controversial. In particular, this paper establishes that the cytotoxic factor is a circulating antibody which, though independent of antibody to thyroglobulin, is closely associated with or identical to circulating complement-fixing antibody directed against thyroid intracellular antigen.

Variation in Susceptibility of Cells Derived from Human Thyroids of Varying Pathology

While the cytotoxic factor is specific for thyroid cells, not all thyroid cells are equally susceptible to its action (Irvine, 1960b, 1961a). Cells derived from hyperplastic goitres have invariably been susceptible, provided they are tested within the first 24–48 hours in culture and that complement is present in adequate amounts. On the other hand, cells derived from simple colloid goitres have been poorly or frankly non-susceptible to cytotoxic factor.

It is now possible to express this variation in quantitative terms by testing cells derived from different thyroid glands against cytotoxic sera which had previously been shown to be capable of giving titres as high as 1:10,000. Such sera will be referred to hereafter as "standard" cytotoxic sera. Using such a serum the susceptibility of cells from different thyroids was graded by noting the highest dilution of serum at which a cytotoxic effect could still be observed. The results are illustrated in Text Fig. 1, where it is seen that cells derived from thyrotoxic glands often give titres greater than or equal to 1:10,000, while cells from "normal" tissue (derived from a histologically normal thyroid gland during parathyroidectomy and from thyroid tissue remote from a simple thyroid cyst) gave titres of 1:100 and 1:1,000 respectively. Cells from non-hyperplastic nodules or colloid goitres gave titres that were either negative or weakly positive (1:10).



TEXT FIG. 1.—Susceptibility of thyroid cells to cytotoxic factor correlated with pathology of gland of origin. Each cross represents a separate gland.

The few thyroid carcinomata I have had the opportunity to study have been difficult to trypsinize, and in only one instance has it been possible to do a satisfactory titration experiment. The histology of this particular gland was that of an adenocarcinoma. Its trypsinized cells were not susceptible to a serum which was known to contain cytotoxic factor in high titre. However, tumours of different histology might well behave differently both in respect to the ease of getting their cells into suspension and in respect to the susceptibility of these cells to cytotoxic factor.

It was noted previously that cells derived from a Hashimoto gland were susceptible to cytotoxic factor,