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PYOGENIC OSTEOMYELITIS: THE INFLUENCE OF BONE REMODELLING ON RECURRENCE
H. M. Frost, M.D.*

INTRODUCTION

It is known that streptococcal and pneumococcal pyogenic osteomyelitis exhibit a strong predilection for infants and that recurrences of these two entities in infants is uncommon. It is known that staphylococcal pyogenic osteomyelitis exhibits a predilection for older children and adults, and that recurrences are more likely than when the etiological agent is a streptococcus or pneumococcus. Recurrences are more likely when the disease occurs in the adult. Recurrence in osteomyelitis affecting cancellous bone, such as vertebral body, is less common than recurrence in osteomyelitis affecting cortical bone.1,2,3,4,20,21

Previous publications have pointed out that the normal bone spaces,** numbering over 1,000,000 per cubic millimeter of cortex,10 act as a bacterial reservoir in pyogenic osteomyelitis. Microorganisms invading bone infest all of these spaces until their source of nutrients—dead cells and tissue — is exhausted. At this stage the streptococci and pneumococci seem to die off, explaining the low recurrence rate and the more benign aspect of these infections as compared to staphylococcal ones. Staphylococci manage to survive in the bone spaces in some manner, perhaps as protoplasts, and can remain potentially infective for observed periods as long as 70 years. This bacterial reservoir of pyogenic osteomyelitis' makes staphylococcal osteomyelitis and perhaps osteomyelitis due to a few other bacterial agents, peculiar.

Diffusion impedence is the resistance to diffusion from one point to another experienced by molecules in a solution.*** A high diffusion impedence normally occurs in fresh bone in vitro. A high diffusion impedence has been observed in bone with the tetracycline antibiotics in man in vivo. It is probable that this diffusion impedence affects other antibiotics in bone also.11,15 Diffusion impedence is particularly high in the case of bone that is dead in vivo.5,6 It is probable that the prolonged antibiotic dosage empirically found necessary in treatment of pyogenic osteomyelitis is due primarily to the high diffusion impedence affecting the antibiotics in bone. It is thus likely that with short dosage times the spaces of the bacterial reservoir of pyogenic osteomyelitis do not develop sufficient concentrations of the antibiotic to sterilize them.

In this paper the effect of remodelling on the bacterial reservoir will be pointed out. By remodelling is meant the sum total of bone formative and destructive processes. These processes may be considered in two parts. The first comprises the internal remodelling which goes on for the duration of life and which is gradually responsible for the removal of old bone and replacement by new bone. The second comprises the more active, and morphologically more distinctive, processes associated with growth.

It will help in the following discussion if the reader will visualize the portion of the bone involved in osteomyelitis as being distinctively labelled. In actuality this

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**These spaces are the marrow spaces, vascular channels, osteocyte lacunae and canaliculae.
***The solution may be gaseous or solid as well as liquid.
part of the bone is distinguished by greater numbers of dead osteocytes and dead vascular channels, and by the presence of microorganisms in these spaces. In an analogous sense this dead, bacteria-containing bone may be thought of as labelled a bright yellow. The effect of remodelling processes on this yellow, labelled bone may then be visualized as a removal of it and replacement of it with unpainted, uncontaminated, live, normal bone. There is more to this analogy than mere speculation. The recently discovered labelling of bone with tetracyclines produces such an effect in vivo which is permanent until remodelling processes remove the labelled bone, and which can be observed and measured for observed periods as long as 9 years between labelling with tetracycline and examination of the skeleton at post-mortem. It is with the aid of tetracycline labelled human skeletons that the essential information given in the following paragraphs was obtained.†

**REMODELLING**

*Internal Remodelling and the Bacterial Reservoir of Pyogenic Osteomyelitis*

For many years it has been realized that a ceaseless destruction of existing bone, and replacement with new bone, goes on in the skeleton regardless of the age of the person. The rate at which this internal remodelling and reconstruction occurs has been a matter of guesswork and of analogy from animal to man. Prior to recent methods and work the normal, internal remodelling could not be measured in man.

It has been learned that normal, internal remodelling is characterized by the elaboration of osteoid seams during the formation of lamellar bone,⁸,¹³ that lamellar bone is the normal adult skeletal constituent, and that the formation of osteoid seams and the formation of tetracycline labelled bone bear a reasonably constant relationship to each other.⁸ Armed with this information, and additional data which need not be elaborated here, it has been possible to measure remodelling activity in man in terms of new bone formation.¹² A representative curve of remodelling activity in human rib by age is given in Figure 1. At two points on the curve a quantitative measurement is designated in terms of the percentage of the absolute bone volume that is torn down and remade per month. It will be seen that internal remodelling is very active at one year of age but slows down markedly during adulthood, being lowest about age 30. If we express remodelling rates in terms of the biological half-life of the bones, the figures are more meaningful. At age one year the half-life is about .25 year, while at age 30 it is 15 years and at age 60 about 8 years. At age one, a year of normal remodelling will remove over 93% of the contaminated bone that is called the bacterial reservoir, and replace it with normal, uncontaminated bone. At age 30 a year of normal remodelling will remove less than 5% of the bacterial reservoir.

It can be seen that the active remodelling processes of the very young will remove nearly all of the bacterial reservoir, given sufficient time; that this removal will be

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†It should be understood that in many instances tetracycline labelled material has merely confirmed estimates made by other means, or analogies made from animal investigation.

‡‡Absolute bone volume: the volume of bone remaining after subtraction of the volumes of the osteocyte lacunae and canaliculae (about 2%), the vascular channels (5-10%) and the marrow spaces.

+++The time required for remodelling processes to reconstitute half the absolute bone volume if remodelling continued (at the measured rate) indefinitely.
Frost

less complete the older the child at age of onset of his disease; and that the contami­
nated bone will never be completely removed by this means. A moment's reflection
and an analogy will reveal why. There was once, in Greek mythology, a hare who
ran a race and who covered first half of the distance, then half the remaining distance,
then half that remainder and so on to infinity, so that in the analogy he never made
the finish line. In the present case, the analogy happens to be true rather than fallacious.
During a normal life there would always be some contaminated bone remaining,
unremodelled.

In the above discussion several factors have been omitted but must now be
mentioned for the sake of completeness. First, there is great individual variation in
remodelling rates among different patients. Second, a thoroughly sequestered
piece of cortex does not undergo much internal remodelling, although in time it
may be completely destroyed or evacuated. Third, in the presence of adjacent in­
fection the remodelling rate in a bone increases so that the values given in Figure 1

![Figure 1](image)

Osteoblastic activity in ribs and clavicles plotted against age. The activity was measured as
seams/mm² of cortex in 40 clavicles and 65 ribs. While the "Y" axis is a linear plot, the "X" axis
is logarithmic. There is a rapid decrease in internal remodelling activity in the first 20 years of life.
By planimetric methods applied to human, tetracycline labelled bone, it is known that the bottom
dot on the rib scale corresponds to a biological half-life of 0.25 year, while the 5th dot from the
top corresponds to a biological half-life of 8 years.

(Reproduced by permission Henry Ford Hospital Medical Bulletin, 9, 1961)
Pyogenic Osteomyelitis

are low for what would be expected in the case of pyogenic osteomyelitis. A case in point is the fibula of a 47 year old man. There was an osteomyelitis of the tibia. The half life of the femur in this extremity was 47 years while that of the fibula was 2.3 years, the latter being a very high rate for a bone of the appendicular skeleton in an adult.

Growth Remodelling and the Bacterial Reservoir of Pyogenic Osteomyelitis

The second type of remodelling is that due to growth and so is peculiar to children. The effect this will have on the amount of bacterial reservoir remaining after an attack of osteomyelitis, and the effect of the age of the child at the time of onset of the disease, is illustrated in Figure 2. A representative bone, the tibia, is viewed in both cross and longitudinal section at age one, two and 7 years. The original, contaminated bone is shaded. It is seen that as the diameter and length of the bone

Effect of Remodeling due to Normal Growth

Figure 2

Diagrammatic presentation of the effect of growth on the composition of older bone — the left diagram is that of a tibia of a child one year old, seen from the front and in cross section. On the right the effect of 6 years of growth is seen in similar views. The cortex of the one year old has been completely removed by age 7. Accordingly any bacteria residing in osteomyelitic bone at age one would be removed entirely by age 7 and so could not cause a recurrence of osteomyelitis.
Frost

enlarge due to growth, the original bone is progressively removed. All of the bacterial reservoir would be removed provided the child were young enough at the time of onset of the disease, or provided the amount of contaminated bone were sharply limited by vigorous early treatment of the disease, by low virulence of the organism, by high resistance to the infection and by other factors. In some cases the disease might be so advanced before it is arrested that a degree and type of damage would result which prevents subsequent growth remodelling from removing all of the bacterial reservoir. It can be appreciated that in the older child it is less likely that growth remodelling will remove all the bacterial reservoir, and that near skeletal maturity this is impossible.

DISCUSSION

The course of any single case of pyogenic osteomyelitis is the result of interplay of so many different factors that it will be very difficult to recognize, evaluate and assign quantitative importance to all of them. In this paper and its predecessors an attempt is made to discuss and bring to the clinician's attention some pertinent newer information. The significance of this information on the pathogenesis and course of the disease must be discussed.

The basic source of bacteria for recurrence of pyogenic osteomyelitis is the bacterial reservoir present in the physiologic spaces of contaminated bone following an attack of pyogenic osteomyelitis. In the case of bacteria such as streptococci and pneumococci, exhaustion of the culture medium apparently brings on the death of the organisms, because recurrences are rare when these organisms are the etiological agent. Staphylococci are different, being able to survive in some manner for many years in contaminated bone.

As a result of these peculiarities three generically different types of phenomena become of interest when dealing with the residuals of a staphylococcal osteomyelitis. The first is the sensitivity of the organism in its peculiar dormant state to antibiotics. This sensitivity may be quite different from the sensitivity of the actively metabolizing organisms in an active infection. This matter is better considered by the bacteriologist than the pathologist.

The second genus of phenomena may be summed up in the term “diffusion impedance.” The antibiotic molecules do not permeate bone as readily as they permeate soft tissues, and in particular they do not permeate dead bone very well. This makes it difficult to obtain adequate concentrations of antibiotic agents in the multitude of spaces in contaminated bone that contain viable organisms. It is easy to visualize a nest of staphylococci, in dormant but viable form, suddenly activated years after the initial attack of osteomyelitis when remodelling processes remove the wall of their bony sarcophagus and thus expose them to the normal body fluids with their contained nutrients. Sterilization of the spaces in the bacterial reservoir becomes a matter of prolonged treatment with antibiotics. In the future it may also become a matter for antibiotics whose physicochemical properties are tailored to the peculiarities of the task.

The third genus of phenomena has already been discussed, and consists of the gradual removal of the bacterial reservoir by internal and growth remodelling. The
latter is the more effective process. This explains the increasing frequency of recurrence of staphylococcal osteomyelitis with increasing age of the patient at the time of onset.

SUMMARY

The existence of a bacterial reservoir inhabiting the normal spaces in bone after an attack of pyogenic osteomyelitis has been noted. The peculiar ability of staphylococci to remain in these spaces in a potentially infective state for many years has also been noted.

The internal remodelling of bone that occurs all during life gradually removes this bacterial reservoir and replaces it with healthy, uncontaminated bone. This process is much more active in children than in adults. It has recently become possible to measure it quantitatively. The remodelling rate may be expressed as the number of years required to reconstitute half of the absolute bone volume. In these terms, normal biological bone half-lives are, at age one: 0.25 years, age 30: 15 years, age 60: 8 years. While internal remodelling is relatively effective in removing the bacterial reservoir in children, it is relatively ineffective in adults but could not completely remove the bacterial reservoir in either. There normally is some acceleration of internal remodelling in bone adjacent to dead, osteomyelitic bone so that the figures given are in reality low in the presence of the disease being discussed. In sequestered bone, remodelling is nil for practical purposes. A sequestrum must be destroyed or evacuated.

Growth remodelling is capable of completely removing the bacterial reservoir. This is more apt to occur when the onset of the disease is early, when treatment is early and vigorous, when other factors act to minimize the amount of bone contaminated, and when the disease does not markedly interfere with subsequent growth remodelling.

REFERENCES


