In Vivo Impermeability Of Feathered Bone To Tetracyclines

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IN VIVO IMPERMEABILITY OF FEATHERED BONE TO TETRACYCLINES*

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INTRODUCTION

The existence of an incompletely mineralized state of some bone matrix in man in vivo has been separately reported. This incompletely mineralized state has been termed feathering and is not causally or essentially related to osteoporotic states or osteomalacic states of bone. Serum chemical values of calcium, phosphorus, alkaline and acid phosphatase are usually normal in patients with severe degrees of feathering.

It has been reported that feathered bone in vitro is highly permeable to a large number of inorganic and organic reagents tested in this respect. Milch, Rall and Tobie deserve the basic credit for noting and publishing the fixation of tetracyclines in bone. The use of tetracyclines in vivo in man to label bone and explore some aspects of permeability and diffusion impedence in bone has been reported. This paper describes the in vivo impermeability of feathered bone to tetracyclines, a result diametrically opposite of that expected.

MATERIAL

In the Henry Ford Hospital Orthopaedic Research Laboratory case material, sections were reviewed from 43 patients who received tetracyclines during life. Of these 43 cases, drug dosage had ceased in 37 cases two or more days before death or the surgery from which the specimen was obtained. In 6 cases tetracycline administration continued up to the time of death.

The cases in which drug dosage stopped some time before death or surgery supply material from which we can learn where and in what quantity tetracyclines are permanently fixed in bone.

The cases in which drug dosage continued up to the time of death or surgery supply material from which we can learn where and in what quantity tetracyclines reversibly stain tissue but from which they disappear upon cessation of drug dosage.

METHODS

For the present purpose a microfluorescence set-up was used to detect the presence of tetracyclines. The microfluorescence method is much more sensitive than detection of tetracycline with bright field technique. Consult refs. (4, 6) for fuller details.

With microfluorescence methods tetracyclines appear white, yellow or yellow-orange on a green to magenta background. They are readily recognized in suitably prepared material by their color. Only a few cases have been found where other substances administered to patients in vivo cause fluorescence in suitably prepared material.

From the bone specimens submitted for examination thin, undecalcified sections

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were made, stained with basic fuchsin and mounted according to the writer's techniques, which should be closely adhered to for this type of work.¹ ²

OBSERVATIONS

A. Cases where tetracycline dosage continued to time of death or surgery:

Detection of tetracycline in these patients' tissues indicates two things: A diffusion pathway was open to the tetracycline molecules in the blood, and some mechanism existed for attachment of considerable numbers of these molecules to the material where fluorescence is observed.

New Bone⁶ Tetracycline is detectable in over half of the fuchsin-permeable portions of new bone. There is a distinct perilacunar preference for the maximum observable concentration of the drug.

Feathered bone² On the average only about 5% of the feathered osteons in these cases exhibited any detectable fluorescence. Since the new and feathered osteons were observed in the same sections, vagaries of technique cannot account for the difference which must be real rather than artifact. There is, of course, a limit to the amount of tetracycline which can be detected in bone by microfluorescence. We do not know quantitatively what this limit is, but it is on the order of millimicrograms when proper microscopic technique is exercised.

B. Cases where tetracycline dosage stopped some time before death or surgery:

New Bone: No tetracycline can be detected by the means utilized in any new bone in these 37 cases.

Feathered bone: A small percentage of feathered osteons contained detectable tetracycline. The percentage varied, but is on the order of 0-7%. The majority of feathered bone revealed no tetracycline. Interestingly, sizable numbers of osteons were observed in which the feathered portion revealed no tetracycline while the normally mineralized portion revealed a tetracycline band, indicating the osteon was in the formative process during drug dosage. This enables us to date such osteons if we know when the drug was given. In the two oldest cases, tetracyclines had been administered 6 years before death and the bands are still present, though faded somewhat. Several of these 6 year-old osteons are also feathered, proving conclusively that feathered bone is not necessarily new bone.

DISCUSSION

The foregoing observations indicate that the vast majority of feathered bone in man is not permeable to tetracyclines in vivo. With due caution in interpretation, this phenomenon suggests that some diffusion barrier exists in feathered bone which might

(a) Considered to be new by criteria of the presence of osteoid seams lining the vascular canal or by empty lacunar counts of 2% or less. See references (3, 7) for details.
(b) Considered to be feathered according to the criteria in reference (3).
(c) The multiplicity of factors which may affect bone permeability and blood-bone exchange are discussed elsewhere but make an assumption of equivalent behavior between tetracycline and other molecules rather dubious without any corroboratory evidence.
Impermeability of Feathered Bone

also affect the permeability of feathered bone to other substances such as lead, strontium, calcium and the normal electrolytes and buffers found in the blood.

Such a diffusion barrier might also help to explain how feathered bone can exist in the skeleton for such long time periods. Current thinking indicates that, once mineralization of the matrix is initiated, it should continue progressively even in the absence of living bone cells, as long as normal body fluids bathe the bone. If this were the case, how could old feathered bone exist? A diffusion barrier between the feathered bone and the vascular fluids would explain the situation, at least in part.

Nothing outlined in this paper suggests itself as an explanation for the diffusion barrier hypothecated.

SUMMARY

Using in vivo staining of bone with tetracyclines, it has been found that feathered bone in vivo is, for the most part, impermeable to tetracyclines. This suggests that in vivo some diffusion barrier exists which isolates feathered bone from the blood. It has also been learned that at least some feathered bone is 6 years old.

REFERENCES