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Allergy and the bone: connections

The review by Gatti et al¹ entitled “Allergy and the Bone: Unexpected Relationships” in this issue of the *Annals* seems to fit the theory advanced in James Burke’s BBC show “Connections” that scientific progress is nonlinear and comes from a series of seemingly unconnected events that then can be connected.

The review stimulates thinking about our understanding of how the body uses mediators in multiple roles and how our treatments of one disease can affect an often unrelated organ system. Clinical medicine is full of these examples, such as finding that the antihypertensive minoxidil might benefit male pattern baldness.

There is an anabolic role of prostaglandins in bone metabolism.² Should we have long-term concerns with the CRTH2 antagonists now being studied to treat allergic rhinitis and asthma? Will there be sufficient blocking of prostaglandin D₂ activity to affect bone density?

The review also highlights the difficulty of maintaining “primum nocere” in treating patients. Active agents appear always to have unexpected side reactions. The decision now is whether the benefit is worth the risk.

The most obvious connection between bone and allergy is through vitamin D. It is beyond the scope of an editorial to thoroughly review all of the recent vitamin D information. I have included references for those who want more information.^{3–5} For this editorial, I have chosen select actions and associations that relate to allergy. I must preface my comments with the caveat that there are many confounding issues to be resolved.

One basic action of vitamin D through its biologically active form, 1,25-(OH)₂-vitamin D, and the vitamin D receptor is inhibition of dendrite cell maturation, with augmentation of interleukin (IL) 10 production while downregulating IL-11 and upregulating IL-12, which promotes a shift from the T_H1 to a T_H2 phenotype.⁶

Vitamin D supplementation of healthy human volunteers increased the percentage of T-regulatory cells by approximately 20%, when 25-hydroxy vitamin D (25-OHD) levels were doubled.⁷

Serum 25OHD levels were inversely associated with the number of positive aeroallergen skin test results and total serum IgE levels in asthmatic children. The levels were positively correlated in asthmatic children with lower forced expiratory volume in 1 second and ratio of forced expiratory volume in 1 second to forced vital capacity. The need for inhaled or systemic corticosteroids for asthma treatment increased with lower 25-OHD levels.⁵

In vitro treatment with 1,25(OH)₂-vitamin D can reverse corticosteroid resistance. In vivo vitamin D supplementary treatment of corticosteroid-resistant patients enhanced the IL-10 expression by CD4 cells.⁸

In a mouse model of allergen immunotherapy, 1,25(OH)₂-vitamin D₃ potentiated the efficacy, which was associated with increased IL-10 and transforming growth factor β .⁹

The big question is whether vitamin D deficiency and alterations in immune regulation can explain part of the documented increase in allergic disorders. In the National Health and Nutrition Examination Survey (NHANES) study, there was a near doubling of vitamin D insufficiency. From 1994 to 2004, only 25% of the current NHANES patients achieved sufficiency levels (25-OHD level greater than 30 ng/mL). The problem was greater in the minority population, with vitamin D insufficiency in more than 90%.³

Measuring 25-OHD levels should become part of our initial allergy workup, with replacement therapy for patients with insufficient or deficient levels.

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The 10-second rule and other myths about epinephrine and autoinjectors

This issue of the *Annals* contains a short, elegant study entitled “The TEN Study: The Time Epinephrine Needs to Reach Muscle.”¹ Its major contribution is to show that the instructions to hold an automatic epinephrine injector in the thigh for a count of 10 that appear in the patient information pamphlet for all automatic epinephrine injectors available in the United States are misleading, because the full dose of epinephrine is, in most instances, delivered within 3 seconds.

The beauty of the study lies not only in the design, but in the fact that the investigators had the imagination to challenge dogma, dogma so prominent that many investigations, cited in this article, have used the 10-second rule to demonstrate that not only patients, but also physicians, have failed to use automatic epinephrine injectors properly.

The irony in their discovery is that in actuality we have known, probably since the inception of the epinephrine autoinjector, that the entire dose was delivered within 3 seconds. This was called to my attention many years ago when I was asked to review an anaphylactic death that was initially blamed on the fact that the patient in question withdrew the automatic injector before 10 seconds. I was sent the data from what was at that time Meridian Laboratories regarding the injection time, and it was quite clear that the entire dose was administered in less than 3 seconds in almost every instance, confirming the data obtained in the “TEN Study.”

False knowledge can persist unchallenged and alter our behavior in doing so. However, other points of importance are brought to the forefront by this innovative article. They have to deal with what other “myths” are circulating regarding epinephrine and automatic epinephrine injectors.

The authors allude to 1 other possible misconception in their discussion. Studies have shown that the needle length of automatic epinephrine injectors may be insufficient to reach the vastus lateralis muscle and therefore fail to deliver the dose intramuscularly.^{2,3} However, the end of the needle is not the final depth achieved by the injection. Epinephrine is delivered under pressure. The authors of this study determined that the pressure behind the injection averaged 14.6 mmHg. This pressure may be sufficient to drive epinephrine into the muscle despite the fact that the needle length itself does not reach the vastus lateralis. This is in keeping with results obtained by analyzing the delivery depth of epinephrine given by an autoinjector into the subcutaneous tissue of swine,⁴ which demonstrated that, compared with a needle length of 1.3 cm, the delivery depth of epinephrine was 2.69 ± 0.5 cm ($P < .001$).

Another possible misunderstanding regarding epinephrine is “the optimal dosing regimen.” In actuality, no one knows what the optimal dosing regimen is. The authors mention this in their introduction. The dose delivered by automatic epinephrine injectors recommended for anyone weighing 30 kg or more is 0.3 mg. How this dose was derived, at least to my knowledge, is unknown. However, before the advent of currently available automatic epinephrine injectors, the dose of epinephrine recommended for treatment of asthma in adults was up to 1 mg, and the dose for an infant weighing 25 pounds was 1/6th of the adult dose.⁵ Variations of this dosage (0.2–0.5 mg) were recommended for the treatment of anaphylaxis at least as late as 1978.⁶ Indeed, an automatic epi-

Disclosures: Advisory Board for Dey Pharmaceuticals; Consultant for Dey Pharmaceuticals; Consultant for MEDA Pharmaceuticals; Consultant for Sanofi-Aventis Pharmaceuticals.

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