Comparative Immunology in Pediatrics Revisited
(Being a Contemporary Analysis of the Paper
Written on this Subject by Dr. James D. Trask in 1928)

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Medical mysteries get solved at a remarkable rate these days. This is particularly true when the mysteries involve mechanisms rather than therapeutic stratagems. Of course, the scientific force tackling these cases is larger than ever and certainly better equipped and trained than in previous ages. Medical detective work is incredibly expensive but, with arguments about priorities excluded, few would doubt the quality of the benefits so bought. There remain, however, a number of problem cases that still defy solution despite the collection of ever-increasing pieces of the jigsaw puzzle.

There is little doubt that authors in 2028 reviewing medical concepts puzzled over in 1978 will experience two reactions. They will look condescendingly at the concepts of earlier colleagues who all in all did remarkably well in the scientifically primitive 1970s. However, these future reviewers will probably feel some disquiet as they realize the fact that certain basic questions that they found raised in the 1970s have answers that are still unknown. The 1920s that are fifty years past have provided an article for contemporary comment that is the purpose of this paper but engendered in this reviewer the reactions outlined above.

In Volume 1 of The Yale Journal of Biology and Medicine (1928–1929), Dr. James D. Trask¹ tackled the subject of comparative immunology in pediatrics. It makes fascinating if difficult reading for the modern physician/immunologist. Fashions change, and both the style of writing and the diseases discussed have largely disappeared from our environment. The disappearance of the former has many regrettable aspects. Trask's style is verbose by modern standards and speaks for an editorial largesse not likely to be accorded this comparator. With a few "dear readers" scattered around we could have an "O'Henry" style discourse that, while admittedly unnecessary, has a cultured ring to it and emphasizes the art as well as the science that is medicine. Such phrases as "cannot at present be answered positively," "it might be pointed out," and "... warrants the serious consideration of another hypothesis," have long since departed from medical literature.

The author was concerned with three subjects in this paper. The first was

¹Trask JD: Comparative immunology in pediatrics. Yale J Biol Med 1:1–7, 1928

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summarized at the end of the paper: are the "artificial boundaries" that limit a physician's practice to Medicine, Pediatrics, Obstetrics, etc., detrimental to medical progress? Clearly, the warning he sounded then is even more relevant today. The problem has been compounded, so compounded by the development of knowledge that the application of these advances in medicine can only be delivered by further medical compartmentalization. This conventional wisdom worries many of us and it is unlikely that our present habits would be regarded as improvements by Dr. Trask.

He would, however, be delighted and even amazed by the advances that have occurred in a second area that concerned him as the 1920s closed. Why, he lamented, are not the immunological approaches so recently espoused by Elie Metchnikoff being applied to clinical studies of immunological problems? Immunology in Trask's context meant natural and provoked host defense mechanisms against infectious agents. He points out that much had been learnt by phylogenetic comparisons. The response to similar antigens amongst many vertebrate and invertebrate subjects had been shown to vary enormously. Metchnikoff had even provided evidence for infectious diseases amongst plants. Immunology, said Trask, was concentrating too much on preparing pure bacterial antigens and not enough on the variability of the host's response to these antigens. Could not a child's immune response be as different from an adult's as the response of invertebrate hosts is to that of vertebrates?

Modern immunologists have constructed a remarkably detailed picture of the phylogenetic evolution of our immune system. We now know that biological systems use defense mechanisms that range from non-specific phagocytosis, first observed when Metchnikoff introduced a rose's thorn into the protoplasm of a primitive jellyfish, to specific mechanisms that can harness all inflammatory processes, exhibit memory, and can distinguish with unbelievable sensitivity self antigens from foreign antigens. Of the two weapon systems that comprise our immune system we know that cell-mediated immunity is phylogenetically older, being present in primitive earthworms. Humoral immune mechanisms that result in antibody production represent a more recent addition to our defenses. It was in the primitive sharks with their primitive IgM-like molecules that nature first experimented with an antibody system whose evolution was clearly pressured by the success being enjoyed by pathogenic bacteria. Trask and similarly interested contemporaries would surely be fascinated to know that modern immunology, having observed the phylogenetic development of specific immunity by comparative immunological studies, can now see the whole complicated and wondrous achievements of many a millennium repeated in every human embryo where phylogeny is recapitulated in ontogeny in a 16-week period.

It was Metchnikoff's colleague and co-Nobel prize winner, Paul Ehrlich, who proposed that cells (lymphocytes) must be genetically programmed during fetal life while remote from antigenic encounter so that they might possess cell surface receptors that would allow any one cell to recognize but one antigen. With this antigen bound to its surface a cellular response would follow that would specifically eliminate the offending antigen. It took more than 60 years of investigation to prove Ehrlich's hypothesis but it is now the cornerstone of modern immunological knowledge. If the cell encountering antigen was educated in the thymus, we get a cell-mediated immune response (e.g., delayed hypersensitivity). If the cell was educated in the bone marrow, it divides to form a plasma cell that secretes antibodies. Clinical immunologists can now diagnose defects in what is normally an obligatory maturational sequence that provides us with the capacity to produce a heterogeneous immune response. Congenital immune deficiencies are in fact classified according to this concept.
If we were comparative in the above sense, we are now entering a phase of comparative immunology recognized as essential by Trask but expanded far beyond his original concept. Study variability of the host's response, he urged; what is the effect of age on the immune response; why do we have individual variability to antigenic stimulation?

It can be stated confidently that the major thrust of modern immunology at both the basic and clinical level is designed to answer these very questions.

We know that the immune system deteriorates with age and we know that it deteriorates faster in some individuals than others, but, like Dr. Trask, we believe that the "variability of the host" is most important in the area of immunoregulation. Suspicions of a thymus-dependent system had not developed in 1928 but in the 1970s we are preoccupied by a study of one of at least three types of cells produced by this gland. Apart from the effector cells that provide an inflammatory response known as delayed hypersensitivity, and which protect us from viral and fungal infections amongst other things, we have another "T" cell concerned with immunoregulation. This cell acts as an immunological sensor that is responsible for the appropriateness of the effector response provided by both the humoral and cell-mediated systems.

The immunoregulatory T cell seems to function according to genetic information encoded close to the area of the D locus of the sixth chromosome in man. In any two individuals the genes occupying these loci can differ (alleles), and it is becoming increasingly clear that we are not all born equal in this area of immunoregulation. Numerous diseases are now being associated with specific gene clusters in this area. Immunologists have mapped in detail the equivalent area in the mouse and provided enormous amounts of evidence for the genetic control of both immunoregulatory phenomena and antigen recognition skills. Thus, Trask was correct when he suspected that encounters with similar environmental agents could provoke entirely different responses in individual hosts.

The third matter discussed by Dr. Trask raised specific questions about the immune response to three infectious diseases that are no longer of importance clinically in economically blessed countries. Scarlet fever, diphtheria, and tetanus were the diseases chosen for comparison. Scarlet fever seems to have disappeared without any intervention from man and prior to the antibiotic era. The decreases in diphtheria and tetanus have been a direct consequence of man's application of immunological principles to the control of disease by immunization. That these measures are not widely enough applied throughout the world was evident in a recent trip to Africa by the author where tetanus is still a significant problem. Parenthetically, one might also point out that even in developed countries like the United States effective control measures for tetanus, diphtheria, measles, and poliomyelitis are lagging, especially in inner city slums.

Trask is troubled by apparent inconsistencies in the immune response to the toxins associated with these diseases. Had there been more knowledge at that time about species specificity of bacteria, some of his questions regarding the lack of susceptibility in certain animals would have been unnecessary. Again, some of his questions concerning the similarity of human immune responses between mothers and their newborn offspring would have been easily answered had he known that from the eighteenth week of gestation maternal IgG (and only IgG) crosses the placenta so that at birth the baby has adequate adult concentrations of passively acquired maternal IgG in its circulation. The baby is thus capable of making a humoral immune response to all the antigens to which the mother is immune. This antibody has a half-life of 30 days and thus, by the sixth month of life, it has nearly disappeared. If the
baby has not "learned" to make IgM antibodies during this period and is therefore not ready to switch to IgG production, the infant's host defense mechanisms will be severely compromised.

There are, however, some very specific questions that we should try to answer, and it is disquieting that some of these questions cannot be easily answered.

The questions raised concerned the Dick test and the Schick test. The former was used to diagnose the presence of antibodies against the streptococcal erythrogenic toxin that produced the rash of scarlet fever. Subcutaneous injection of cultured toxin produced an inflammatory response unless neutralized by antibody. A similar principle was used with the Schick test, which utilized diphtheria toxin.

The observations that Trask found interesting and inexplicable and yet suitable for comparative study follow. They are all excellent questions.

1. Why is it that only man is susceptible to the scarlet fever toxin? Although rabbits could be manipulated to make them susceptible and could subsequently be protected with antitoxin, man was the only natural victim. We don't know the answer to this first question. Not much work has been done in this area in recent years, probably because streptococci are less commonly producing erythrogenic toxin. Why this should be the case is not clear. The production of the toxin by streptococci is dependent on specific phage infection of the bacteria that alter the DNA of the cell to produce toxin. Of course, there is no certainty that the question could have been answered even if the necessary research effort had been made. We can guess, by extrapolating from similar better known situations, that species-specific receptors for the erythrogenic toxin must exist. These may well be on non-specific cells that are activated to produce an inflammatory response.

2. The study of 200 mothers and their newborn offspring showed that the majority of infants shared the same antitoxin (antibody) status as their mothers. This, no doubt, was due to placental transfer of IgG antibody from mother to fetus. Such infants would not have been expected to develop an inflammatory response in the skin to Dick reagent. However, a few infants with no detectable antibody to the erythrogenic toxin still did not produce a positive response to intradermal injections of the toxin of scarlet fever. This suggested to Trask that neonates could not mount the inflammatory response in the skin seen in older children. He reasoned that as such infants could still suffer from fatal infections with the erythrogenic-producing streptococci, it must be unlikely that the erythrogenic toxin itself was the major producer of the disease's morbidity.

We believe today that he was correct in this latter assumption. While the erythrogenic toxin probably has some effects at sites other than skin, it is not considered to contribute significantly to the potentially serious sequelae of infection with this type of streptococcal organism.

3. Why is it that Dick-positive individuals given toxin for the purpose of developing active immunity become Dick test-negative within 24 hours, days before humoral antitoxin could be demonstrated? There is no answer available for this phenomenon if, in fact, it is true. Little, if anything, has been said about it since that time, and the observation may have been difficult to reproduce. Certainly, we have plenty of examples of antigens, drugs, chemicals, etc., saturating receptor sites and minimizing the effects of second encounters. With cells like mast cells and basophils we can degranulate them slowly by binding an allergen to the IgE on their membranes and prevent them from regranulating by continuing antigenic exposure, thus desensitizing them. In all these examples, however, the initial encounter that desensitizes produces an effect per se. This is not the case if Trask's observations were correct. We do have phenomena in immunology where very large doses of antigen
can exceed the upper threshold for an immune response and cause a state of nonresponsiveness (high zone tolerance) that is not associated with an initial effector response.

4. Can the nasal diphtheria organism which produces only mild illness in young children be the same as that which can be released from the pharynx in adults and children with severe illness associated with toxin production? We can answer "Yes" to this question but between the lines of Trask's queries obviously lies the question, "If so, how come?" Here we can report the fascinating fact that diphtheria exotoxin is well absorbed across the mucous membranes of the pharynx but is only poorly absorbed across the nasal mucosa and by the tonsils. (Why?) Is this a matter of appropriate transport systems, different concentrations of local humoral immunity (secretory IgA) or what? The full explanation will require more work on the subject.

5. Why does immunization against diphtheria on the third, sixth, and ninth days of life fail to produce adequate protection? This, at least is a question we can answer well. The antigen in the infants will combine with maternal antibody and be neutralized before it can be fully immunogenic. The baby, however, is not yet equipped to make his best IgG response and doses so close together would fail even in the absence of maternal antibody. It is interesting that Trask comments on the practice of giving antisera with antigen, a procedure that is still used today; e.g., in giving live measles virus vaccine to young children. Immunologists now have good evidence that such combinations could in fact trigger suppressor T cells and block any chance of making a good immune response.

6. Why are not diphtheria and tetanus toxin general protoplasmic poisons? A dose of tetanus toxoid sufficient to kill 1,000 mice, he reported, won't kill a seven-gram spider. Tetanus toxin, a least, will produce its characteristic effects on the nervous system in most vertebrates, but birds are resistant and frogs only react if you heat them. Here again, we can suggest specific receptor sites for the toxin. Most animals with nervous systems similar to man will be susceptible. But wouldn't you have guessed that birds would be susceptible?

7. Finally, Dr. Trask asked why adult patients at Yale-New Haven Hospital and elsewhere with pneumococcal pneumonia frequently succumbed while children may have a relatively easy time with the same organism? There is no shortage of pneumococcal pneumonia today and in our society the observation is only true if one compares children with debilitated adults. There really is no difference in the handling of the organism by children. We frequently see adults who have smoked, aspirated, and generally abused the macrophages lining the alveoli into a noncombative state. These adults certainly may lose the battle with pneumococcal organisms.

That the above answers would stimulate the mind of a Dr. Trask to produce twice the number of questions is certain. That's fine; after all, good questions are a prerequisite to worthwhile studies that produce useful results. We can but hope that when the editor of the Yale Journal in 2027 decides to get a 100-year perspective applied to Trask's questions, the answers that will appear in the Journal will be complete and reflect the perfected state of the medical arts we can all predict. In the meantime, previously unanswered questions may provoke improved powers of observation and, therefore, make many of us more thoughtful MDs and investigators.

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