November 11, 1974

Dr. E. J. Eichwald, Editor
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Dear Doctor Eichwald:

I return the enclosed manuscript for re-consideration in the light of revisions made at the suggestion of your reviewers. As you suggested, I shall outline what steps were taken to meet their criticisms. I also return a copy of the criticisms with annotations so that you may conveniently follow my responses.

Review I: This review was most kind and the 4 points raised were all resolved.

Review II

1. The revue raises the question of the similarity of the system to the ABO system which is the basic question proposed by the paper, ie can one use a study of natural heterophile immunity to make any deduction regarding the presence or absence of the antigen. We hypothesized that one could and tested that hypotheses in 41 renal transplants. This is discussed on Page , paragraph and throughout pages of the manuscript. We have previously published unequivocal evidence that individuals with anti-HT-A in their sera do not have HT-A in their kidneys (ref. 4 of the bibliography). I fear that the difficulty in establishing the presence of HT-A in tissues was not clear and have added a clarifying statement on the introduction (Page paragraph , final sentence).

2/ The introduction summarizes salient features of earlier work in which the figure of 72% was observed. A clarifying phrase was added to sentence- , paragraph , page . As to which figures are correct, I can only respond by saying that all are correct.

3. Natural immunity is generally defined as that immunity required in the absence of purposeful or planned immunization. We are by definition, reporting in this paper a study of natural immunity in over 900 people. The fact that this natural immunity declined with age is an observed fact illustrated in Figure 2. We do not know its cause nor have we speculated upon it. We said (last sentences, page , first sentence, page) that the discrepency in the incidence of no heterophile immunity in the general population (27.6%) and the population below the age of 21 (15%) was due to the observed decline in immunity with advancing age. The observation is discussed at the where it is specifically stated that the "etiology--is unknown".

4. We certainly do not see how anything we have written would lead to the inference that "only the 15% without antibody possess the appropriate antigen". It is the population with anti-HT-A that does not have the antigen (maximum observed 30%) and the population without anti-HT-A which "possibly does (maximum 70% but certainly less in reality). We discussed this concept on page , paragraph , 80% of page , page - paragraph and page - paragraph

5. The terms which are confusing to the reviewer are clearly defined on page , paragraph of the manuscript. They are used throughout the paper to conform precisely to these definitions. One change was made. We have in the past generally referred to rejections related to heterophile immunity as heterophile rejections. It probably is more precise to term them HT-A rejections. Therefore, the title of the last section in materials and methods was changed to read, "Diagnosis of HT-A rejection". (page paragraph

6. We apologize for omitting a statement regarding the examination of absorbed sera on sheep erythrocytes. This was, of course, always done and the appropriate statement was inserted (Page , paragraph , final sentence). However, it must be recalled that only 13% of human sera agglutinate sheep erythrocytes yet sheep erythrocytes absorb the anti-rat hemagglutinins in a much larger percentage of sera. That phenomenon was discussed in detail in an earlier publication (Bibliography reference)4/) The essential point which the reviewer attempts to raise here is a good one although he has not thought it through. I believe what he meant to ask is, "Since bacterial (or renal) antigens are the homologous antigens, and the sheep and rat erythrocyte antigens are heterologous, why is the phenomenon described not a result of a change in avidity, or a 'narrowing' of specificity of the heterophile antibody, perhaps produced by heightened immunity?"

This is a possibility which cannot be excluded. However, if it is true, there still must be a difference between the heteralogous sheep and rat erythrocyte antigens, to account for the difference in absorption characteristics of the sera, ie the reactive sites on these cells may be very similar but do differ. Thus, when the antibody population of a serum is such that it fulfills our criteria of containing anti-HX-A and anti-HT-A it can be said to contain two spedificities even though it is produced a single antigen. This is in accord with the time honored serologic principle that the spedificity of population of antibodies is determined by the antigens with which they react, not the antigen which stimulated their production.

7. This is an incorrect interpretation by the reviewer which is discussed in Section 4.

8. On Page , paragraph we describe the sera studied and state that sera from transplantation family groups and Acadian family groups were studied.

9. This section, regarding the Diagnosis of HT-A rejection, was clarified.

10. I believe the reviewer questions the propriety of calling Non-HT-A rejection HL-A rejection. He is probably correct and this change was made (Page , paragraph). A clarifying statement was also placed into the discussion (Page , paragraph).

11. These objections are manifestly absurd. This paper is not about rejection in general. It is about heterophile based, or HT-A, rejection. To insist that rejections which occur in the absence of anti-HT-A immunity be used in the analysis of the HT-A system is similar in all respects to suggesting that the effect of pre-transplantation sensitization to HL-A be evaluated by including in the analysis rejection which occurred in the absence of pre-transplantation sensitization.

14. These errors in the text were corrected.

15. It is impossible for anyone who has no heterophile titer to have anti-HT-A. The definition of these terms is on Page , paragraph of the manuscript.

16. Two families are shown in Figure 3. Their significance lies in the fact that the probability of family - a having this pattern of heterophile immunity by chance is approximately .025, that of family - b is approximately .007 (assuming that 30% of the population is HT-A negative and 70% HT-A positive).

17. The legend to Figure 3 has been modified to clarify this point.

18. This statement implies that the entire genetic hypothesis presented in the manuscript was deduced from one HT-A negative offspring. It is such a gross distortion that it must be considered sarcasm. I hesitate to reply to sarcasm but will repeat. We observed the distribution of no heterophile immunity, HX-A immunity, and HT-A immunity in over 900 people. Through simple mathematics we deduced the simplest genetic hypothesis. We applied the hypothesis to the results of 41 renal transplants and demonstrated a surprisingly good correlation which was statistically significant. Finally we tried to disprove the hypothesis by family studies but could not do so.

19. The mathematical appendix is simple. It clarifies our reasoning. It strengthens the hypothesis. I would prefer it remain since it will be helpful to anyone who wishes to ponder it.

20. These concerns have been discussed in other sections.

21. The family studies were performed in an effort to disprove the hypothesis. This cannot be done (nor can the hypothesis be proven) with the present inadequate method of identifying the the presence or absence of the antigen. It can only be condluded that the immune response is genetically based and we have presented the evidence for that statement.

22. Covered earlier.

23. The renal allograft data form the most important part of the paper. It is the only information which tests the genetic hypothesis, and without it we would consider the paper unworthy of publication.

Sincerely,

John C. McDonald, M.D.
Professor of Surgery

JCM:ggf