Increased serum immunoglobulin E concentrations in venereal diseases

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Summary
Total serum immunoglobulin E (IgE) concentrations were determined by a competitive solid phase radioimmunoassay technique in serum samples from patients with a variety of venereal diseases. The mean IgE concentrations for groups of normal persons without venereal diseases was significantly lower than the means for groups of appropriately matched patients with primary syphilis and gonorrhoea. There were also relatively higher IgE values in patients with trichomoniasis. Our data indicate that patients with urogenital infections have higher concentrations of IgE in the serum than matched control patients without such infections.

Introduction
Immunoglobulin E (IgE) functions with more versatility in man than the simple production of allergic diseases (Urquhart, Mulligan, Eadie, and Jennings, 1965; Ogilvie, 1967; Wilson and Bloch, 1968; Ogilvie and Jones, 1971; Steinberg, Ishizaka, and Norman, 1973). IgE facilitates the deposition of antigen-antibody complexes (Benveniste, Henson, and Cochrane, 1972; Benveniste, 1973) in immune complex disease. Through the chemical mediators liberated from mast cells and basophils (Bourne, Lichtenstein, Melmon, Henney, Weinstein, and Shearer, 1974), IgE could also indirectly modify a host's response to infectious agents.

Because of the indications of the broader role of IgE and the reports of the presence of immediate hypersensitivity to gonococcal antigens in gonorrhoea patients (Thomas, 1942), total serum IgE levels were studied in patients with gonorrhoea as the first step in investigating whether IgE participates in a host's response to venereal disease. Subsequently, total serum IgE was measured in patients with trichomoniasis and primary and secondary syphilis infections.

Material and methods
Assay of IgE
Total IgE was quantitated by a solid phase radioimmunosorbent assay (Hunter, and Greenwood, 1962; McConahey and Dixon, 1966; Cuatrecasas, 1970; Levin, Pipkins, and Fudenberg, 1970). Purified myeloma IgE (24 mg./ml.) was generously provided by Dr. K. Ishizaka (Good Samaritan Hospital, Baltimore, Md. 21228). Goat anti-IgE (Fc), absorbed and specific, was kindly provided by Dr. John Wypych (Allergy Research Laboratory, State University of New York at Buffalo School of Medicine, Buffalo, New York 14203). This antiserum contained about 700 μg./ml. of specific antibody. The specificity of the antiserum was confirmed by immunoelectrophoresis and gel diffusion tests. All IgE levels are expressed as units relative to the WHO reference serum 68/341 provided by Dr. Roy Woods of the National Cancer Institute's Immunoglobulin Reference Center in Springfield, Va. The mean coefficient of variation for the radioimmunoassay technique was 21 per cent.

Serum specimens
Sera from non-allergic patients with gonorrhoea (10 males and females) were obtained from patients attending the DeKalb County, Georgia, venereal disease clinic. Control patients for this group, without allergy or venereal disease, were selected from the same clinic and were matched for sex and age.

Sera from randomly selected patients with gonorrhoea were obtained from the DeKalb clinic and from a girls detention home in Atlanta. Serum samples from patients with primary and secondary syphilis had been mailed to the Center for Disease Control (CDC) from numerous sources around the country. Serum from female patients
with trichomonal infections had been obtained at the girls detention home. Unselected control sera for each of the venereal disease groups were obtained from 'normal' employees at the CDC.

The serum from patients with trichomoniasis had been stored at $-70^\circ\text{C}$. All other sera were stored at $-20^\circ\text{C}$. Histories were sufficient to rule out previous venereal infection only in the females with trichomoniasis. This group and the non-allergic patients with gonorrhoea had only one venereal disease at the time the serum samples were obtained. No similar history was available on the randomly selected patients with gonorrhoea or syphilis.

**Results**

Table I lists the number of subjects studied in each patient group, the mean concentration of IgE in units/ml., and the range of values recorded. Fig. 1 is the scattergram from which this data was obtained. Arithmetic means are indicated by the hatched lines. It can be seen that there is a wide overlap of values in each of the groups studied. However, comparisons of the means of the log transformation of this data by Student's 't' test revealed a statistically significant elevation in the primary syphilis group at the 0.009 level (Table II). The IgE concentrations of patients with trichomoniasis were not significantly elevated when compared to the controls. There does appear, however, to be a clustering of higher values in patients with trichomoniasis and in those with primary syphilis.

Fig. 2 is a scattergram for the patients with gonorrhoea without allergy compared to patients without venereal disease and without allergy. It was apparent from our data that a Gaussian distribution was not present; the data were therefore log transformed. Analysis of the means of the log transformation of these data revealed a significant difference at the 0.006 level (Table II). The Mann Whitney U test was also performed on this and on the primary syphilis data and confirmed its significance.

Because the scattergram showed a clustering of higher values in several of the venereal disease groups, the proportion of patients with high values in each of our groups was examined. Fig. 3 shows...
Table I: Summary of mean serum IgE concentrations in different patient groups

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>No. of subjects</th>
<th>IgE (units/ml)</th>
<th>Observed mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeKalb Normals: without allergy and without venereal disease</td>
<td>20</td>
<td></td>
<td>90</td>
<td>10-360</td>
</tr>
<tr>
<td>CDC random normals</td>
<td>60</td>
<td></td>
<td>302</td>
<td>10-2000</td>
</tr>
<tr>
<td>DeKalb: Gonorrhoea patients—without allergy</td>
<td>20</td>
<td></td>
<td>297</td>
<td>10-1050</td>
</tr>
<tr>
<td>Primary syphilis</td>
<td>25</td>
<td></td>
<td>738</td>
<td>29-4050</td>
</tr>
<tr>
<td>Secondary syphilis</td>
<td>25</td>
<td></td>
<td>426</td>
<td>115-3300</td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>40</td>
<td></td>
<td>575</td>
<td>10-4000</td>
</tr>
<tr>
<td>Random gonorrhoea</td>
<td>40</td>
<td></td>
<td>405</td>
<td>40-2100</td>
</tr>
</tbody>
</table>

Table II: Comparison of IgE values for patients with venereal disease and normal control groups

<table>
<thead>
<tr>
<th>Patient group comparison</th>
<th>Mean difference in IgE concentrations (units/ml)</th>
<th>Student 't' test</th>
<th>Mann Whitney U test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhoea without allergy minus DeKalb normals without allergy and without venereal disease</td>
<td>157</td>
<td>0-006</td>
<td>0-02</td>
</tr>
<tr>
<td>Random gonorrhoea minus random normals</td>
<td>102</td>
<td>0-15</td>
<td>0-48</td>
</tr>
<tr>
<td>Primary syphilis minus random normals</td>
<td>431</td>
<td>0-009</td>
<td>0-03</td>
</tr>
<tr>
<td>Secondary syphilis minus random normals</td>
<td>128</td>
<td>0-08</td>
<td>0-23</td>
</tr>
<tr>
<td>Trichomoniasis minus random normals</td>
<td>269</td>
<td>0-13</td>
<td>0-12</td>
</tr>
</tbody>
</table>

This analysis of the percentage of patients in each of the venereal disease groups with values greater than 500 units/ml. (arbitrarily chosen), compared to the controls. Analysis of this data by the \( \chi^2 \) test, comparing the different venereal disease groups with the normal subjects, indicates significance at the 0-005 level for the primary syphilis group and at the 0-025 level for the trichomoniasis group.

Fig. 4 shows a similar bar graph indicating the proportion of patients with IgE concentrations greater than 200 units/ml. in the group with gonorrhoea but without allergy when compared to its normal non-allergy control group. A significant difference was found by Fisher's exact test at the 0-02 level.

Discussion

Our results show that the mean IgE concentration in serum from randomly selected people without venereal disease is significantly lower than the mean concentration from randomly selected patients with primary syphilis. Mean IgE concentrations in serum from patients with gonorrhoea are significantly higher than those of non-venereal disease controls when only patients without allergy are considered. There also appears to be a tendency for higher IgE concentration in randomly selected patients with trichomoniasis. This study suggests the advantage of restricting one variable known to increase total IgE when examining other factors which could influence total serum IgE. This variable is a history of allergy and the value of its restriction became evident when total IgE was not significantly elevated in randomly selected patients with gonorrhoea but was elevated in patients with gonorrhoea but without allergy.

By virtue of the transmucosal route of infection, venereal disease should be capable of eliciting a good IgE response, within the limits of the antigenic stimulus and the individual patient. IgE forming cells have been found at a variety of mucosal surfaces.

![FIG. 3 Percentage of patients in venereal disease groups with IgE concentration > 500 units/ml.](image1)

![FIG. 4 Percentage of patients with IgE concentrations > 200 units/ml.](image2)
(Tada and Ishizaka, 1970) (tonsil and adenoid tissue, bronchial and peritoneal lymph nodes, and respiratory and gastrointestinal mucosa), and IgE is present in a number of secretions including bronchial (Waldman, Virchow, and Rowe, 1973), middle ear (Ishikawa, Bernstein, Reisman, and Arbesman, 1972), lacrimal (Brauningter and Centifanto, 1971), saliva (Ozkara-goz, Smith, and Gokcen, 1972), nasal (Donovan, Johansson, Bennich, and Soothill, 1970; Hubday, Cake, and Turner, 1971), and urinary (Turner, Johansson, Barratt, and Bennich, 1970; Barratt, Turner, and Johansson, 1972; Stokes, Hosking, Turner, and Johansson, 1973). It has not been detected in vaginal secretions (Waldman and others, 1973), but our serum findings in venereal diseases suggest that further investigation by other techniques is indicated.

The clinical significance of elevated total IgE concentration in primary syphilis and gonorrhoea is unknown and cannot be answered from our data. The antigenic specificity of the increased IgE is another unknown. Evidence is accumulating that an IgE response can be mustered to infections agents but with varying results for the host. On the one hand, IgE antibody may help to control infection. This possibility has been lent some credence by the work of Ogilvie (1967) and Urquhart and others (1965), who have shown that, in rats infected with the nematode, *Nippostrongylus brasiliensis*, the formation of IgE-like antibodies in response to the infection leads to the successful control of the infection. It has been postulated that the rat, in order successfully to purg its gastrointestinal tract of the parasite, must form this IgE-like antibody. The antibody, fixed to tissue mast cell, then combines with worm antigen causing the release of chemical mediators. Vascular permeability increases and this causes an efflux of fluids and vigorous contraction of intestinal smooth muscle, which combine to expel the worms from the animal. Therefore, local anaphylaxis in this experimental model is beneficial to the host. The experiments of Steinberg and others (1973) have shown additionally that an immediate hypersensitivity reaction at a local site of toxin injection can lead to more effective neutralization of the toxin than would occur if the immediate hypersensitivity reaction had not occurred. This too is probably due to the increase in vascular permeability and the passage of more antibody to the challenged site.

On the other hand, IgE participation in an immune response may be detrimental to the host and lead to extension of the disease. First, cell-fixed IgE, when combining with antigen, leads to the release of histamine, which stimulates the generation of cyclic AMP in white blood cells (Bourne and others, 1974). In the neutrophil, this blocks the release of lysosomal enzymes after phagocytosis or interferes with chemotaxis. In the T lymphocyte, immune cytolysis and interferon production are impaired. In the B lymphocyte, antibody production or secretion is reduced. Finally, Benveniste (1973) and Benveniste and others (1972) have shown that IgE antibody is important for the development of immune complex disease in the rabbit. In their experimental model, basophils with cell-fixed IgE release a platelet-aggregating factor when IgE combines with circulating antigen. Platelets then accumulate at the endothelial site and release their content of mediators. Vascular permeability is increased and immune complexes, which have been circulating, can now be deposited in the vessel walls and produce tissue damage in this area via complement activation.

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