Hypersensitivity.

The immune response may under certain circumstances result in damaging rather than protective effect. Such a reaction is known as hypersensitivity. The response is exaggerated and inappropriate.

It can be classified into four types :

1)- Type I : mediated by IgE, rapid occurring within minutes of exposure to antigen.
2)- Type II : IgM or IgG binds to cell surface antigen leading to complement activation and destruction of the cell.
3)- Type III : I.C. accumulate and deposit in the circulation and certain tissues leading to complement activation attracting granulocytes and inflammatory damage occurs.
4)- Type IV : delayed hypersensitivity or tuberculin reaction, this is cell mediated : T-cells secrete lymphokines which attract and activate macrophages resulting in local damage.

Type I :

1- sensitizing phase : IgE produced , binds to mast cells.
2- activation phase : re-exposure leads to release of mast cell granules.
3- effector phase : clinical outcome.

1)- Only about 10% of the population develop hay fever, the production of IgE and the clinical response may be MHC genetically linked. IL-4 by CD4 cells is important in switching to IgE. In any event if IgE is produced the person is said to be sensitised. IgE persists on the surface of mast cells for weeks.
The Prausnitz-Kustner reaction is produced by injecting sensitive serum subcutaneously, later exposure to the offending antigen produces a local skin anaphylactic reaction at the site of injection.
IgE is useful in parasitic disease : flushing of the worm (muscle contraction and mucus secretion, ADCC).
IgE production is governed by genetic make up of person, the nature of antigen (usually innocuous), the dose and entry across mucosal surfaces. IL-4 production driving TH2 cells.
Atopy : allergy to various allergens e.g. pollen, fungi, arthropod insects, food, animals.
Anaphylaxis and urticaria : occur in non-atopic patients. Drugs, food, insect bites. IgE mediated.
Some cases of anaphylaxis are not IgE mediated (anaphylactoid reaction): complement activation, radiocontrast exposure, IgG anti-IgA reactions.

2)- Activation phase : wheal and flare , erythema and oedema within 10-15 minutes from injection. Mast cells can be activated by C5a and C3a.

3)- Effector phase : preformed mediators e.g. histamine, serotonin (rat), ECF-A (chemotactic for eosinophils), heparin which is not directly involved in anaphylaxis.
Newly synthesised mediators : metabolites of arachidonic acid, lipooxygenase and cyclooxygenase pathways e.g. leukotrienes (slow and prolonged contraction of smooth

muscle), prostaglandins (bronchial constriction and chemotactic for various leukocytes). Platelet activating factor (aggregates platelets and releases histamine and serotonin from them).

Clinical aspects : localized in skin e.g. mosquito bites, more widespread e.g. hay fever, asthma and anaphylactic shock.

Intervention :

Avoid antigen.

Drugs : antihistamines, steroids (block arachidonic acid metabolism), Na cromoglycate (stabilises mast cell membranes), epinephrine (vasoconstrictor, bronchodilator).

Hyposensitisation : repeated increasing doses of antigen over a period of time , this produces IgG which act as a blocking antibody, also IgE levels drop. (Do not mix up with desensitisation where increasing doses of antigen that do not illicit an anphylactic reaction are given consecutively over a short period of time to deplete IgE before the antigen e.g. anti-venom is administered.

Skin testing is used to detect sensitivity, but RAST is more quantitative.
Examples : allergic rhinitis (hay fever), asthma, insect bite, urticaria, eczema, anaphylactic shock.

Type II hypersensitivity (complement mediated) :

Damage is caused to cells by complement activation, either through lysis or opsonisation.
Simplest form is that seen on incompatible blood transfusion, IgM antibodies cause RBC lysis, resulting in intravascular haemolysis.
In Rh incompatibility, IgG coats the RBC but does not lyse it, because the density of the Rhesus antigen is low on the surface, it acts as an opsonin promoting its phagocytosis, resulting in anaemia and jaundice.
Auto-immune haemolytic anaemia : IgG is produced against own RBC for some unknown reasons leading to haemolysis or destruction through phagocytosis.
Drugs can act as haptens binding to RBC, platelets or WBC resulting in their destruction.
Chloramphenicol-WBC, sedormid-platelets, chlorpromazine-RBC.

Anti-receptor antibodies : blocking effect e.g. in myasthenia gravis (anti-acetylcholine receptor). Graves disease where antibody to TSH receptor mimics its action (this is sometimes known as Type V or stimulatory hypersensitivity.
Other examples are Goodpasture disease and rheumatic fever, pernicious anaemia.
The autoimmune disease may be organ specific or system specific.

Type III :

The prototype of this hypersensitivity is the Arthus reaction, antigen is injected S/C, antibody is injected I/V, diffusion of antibody towards antigen through vessel wall lead to deposition of I.C. at vessel wall, with complement activation and chemotaxis of neutrophils leading to a haemorrhagic reaction at the site of injection. Both complement and neutrophils are required.
Deposition of immune complexes in tissues depends on several factors :
1)- Size.
2)- Extent of clearance e.g. by complement, deficiency of complement predisposes to immune complex disease, or overwhelming of the mononuclear phogocytic system due to persistence of antigen, defective C3b receptors on RBC in SLE.
3)- Charge and affinity.
4)- haemodynamic factors.

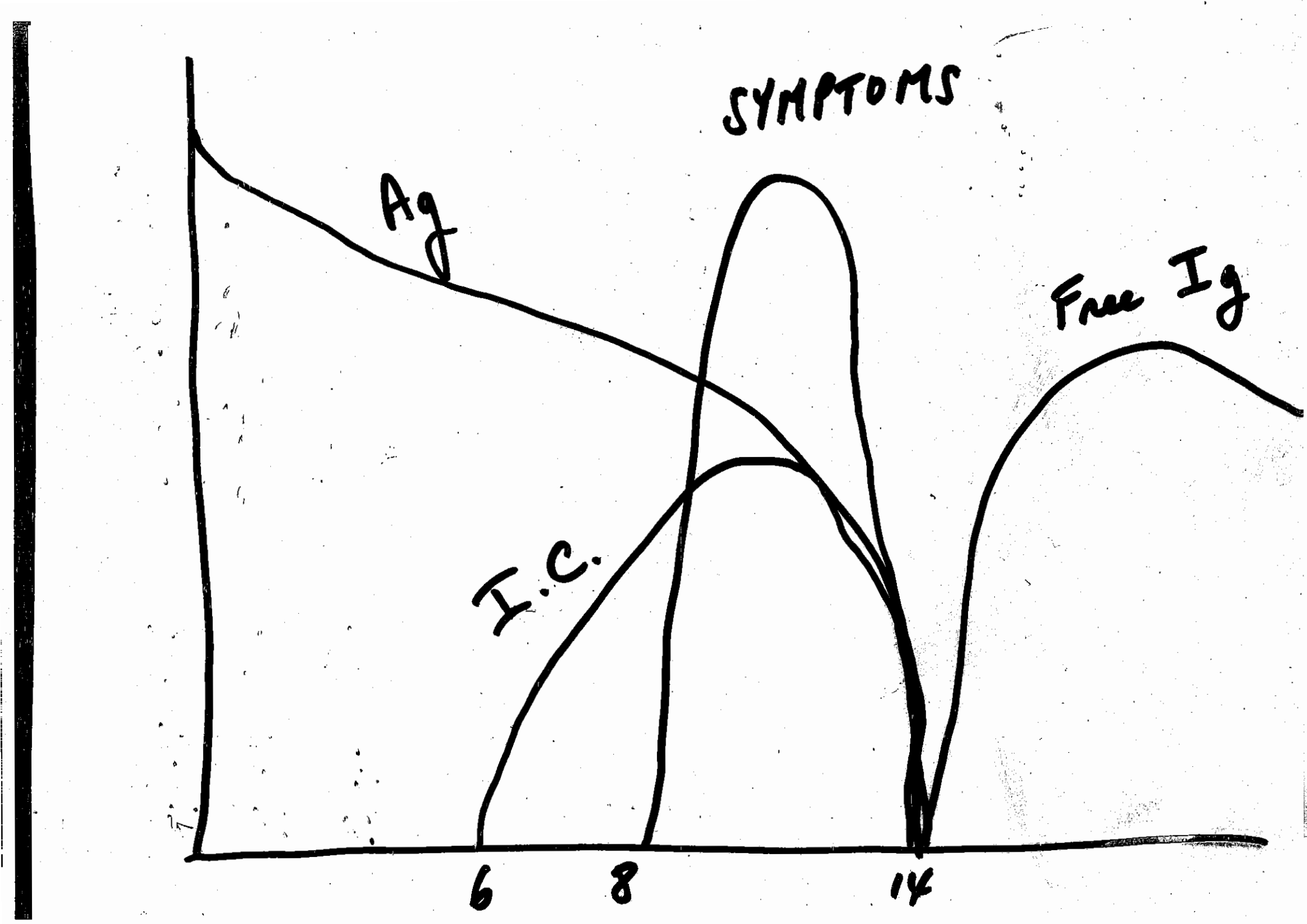
Another example of type III reaction is serum sickness
Graph.
Fever, enlarged lymph nodes, rashes, joint swelling, glomerulonephritis.

Disease examples : glomerulonephritis, Rheumatoid arthritis, post streptococcal GN.

Type IV hypersensitivity :

Takes 24-48 hours to develop. T-cells activated by certain antigens presented by APC's, secrete lymphokines which attract mononuclear cells. This used to be called the tuberculin reaction, but now termed delayed type hypersensitivity.
There has to have been previous sensitisation, i.e. there are memory T-cells which upon encounter with the antigen in conjunction with MHC class II molecule become activated secreting lymphokines.
There is erythema, induration, with mononuclear infiltrate with scattered lymphocytes, neutrophils are not prominent. This progresses to granuloma formation if the antigen persists with fused giant cells. This reaction usually disappears if the antigen is eliminated.

Examples : reactions to measles, small pox, herpes (all have characteristic exanthems skin reaction) are all due to cell mediated immunity.
Contact sensitivity (probably a feature of Langerhan's cell antigen presentation).
Allograft rejection : invasion by mononuclear cells, destruction of vasculature and death of graft.
Graft versus host reaction.
Tc cells may cause injury e.g. in some cases of viral hepatitis in humans (with non-cytolytic virus) Hepatitis B virus.


SYMPTOMS
Ag
Free Ig
I.C.
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