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Introduction

By Paul Kollós,

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In his presidential address delivered before the American Association of Immunologists in 1955 A. M. Pappenheimer, Jr. (120) made the following statement:

“Few areas in modern medicine remain so beclouded in
mystery as the so-called allergic diseases. A substantial proportion of the human race each year suffers to a varying degree from asthma, hay fever, food allergies, drug allergies, contact dermatitis, and other unpleasant kinds of allergic manifestations. While there are few who would deny that hypersensitivity reactions, whether of the immediate or of the delayed inflammatory type, are triggered by a reaction in vivo between antigen and some form of antibody, we understand very little of how cellular damage is caused. It has been firmly established, in the case of the hay-fever type of allergy, that serum antibody is involved, and there is an increasing body of evidence which suggests that the type of antibody concerned (atopic reagin) possesses chemical as well as biological properties which distinguish it from the usual type of precipitating antibody studied by the immunologist in the laboratory. But for the inflammatory (tuberculin) type of delayed hypersensitivity, no relationship to any kind of conventional serum antibody has been demonstrated. We can only infer that this type of reaction results from interaction of antigen with some type of antibody because of its specificity and because of the necessity for prior sensitization.

A. M. Pappenheimer, Jr. (120) came to these conclusions after reviewing the results of 60 years of intensive research work in the field of allergy and it seems to me undisputable that his opinion is entirely justified. Some sunrays burst, however, through the cloudy horizon. One is, that nobody seems to doubt that the allergic diseases are a pathogenetical entity; another, that all agree

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that a specific change of the immunological responsiveness of the organism is the connective link between these different pathological states.

The centre about which all ideas and concepts in this field are revolving, is the antigen-antibody reaction. One obstacle to real understanding and progress is that the definition of “antigen”, as well as that of “antibody”, is uncertain and highly unsatisfactory. In fact, we have no definition, merely a “circular set of definitions” (G. Edsall, 1957), since antigens are characterized as substances which induce the production of antibodies in vivo, and antibodies as globulins formed in response to this antigenic stimulation and able to combine specifically with the inciting antigen (36, 77a). It is only too familiar to allergists that it is quite often necessary to widen the limits given in these imperfect definitions and seek refuge
in analogies and hypothetical constructions, in an attempt to coordinate experimental and/or clinical observations. The administration of a given substance for instance, induces the production of antibodies in all individuals of a given species or in some of them, and must be regarded as an antigen. The same substance, however, will not lead to antibody formation if administered under different conditions or to individuals of another species. Consequently, antigenicity is a relative and not predictable property.

The specific changes in the responsiveness of the organism, observed in the earliest studies in this field, concerned the “immune state” which remains after recovery from a bacterial or viral disease. The discovery that the plasma of the immune organism contains a peculiar sort of protein, belonging to the globulin fraction and able to combine with the inciting pathogen in vivo and in vitro, led to the concept that the formation of such “antibodies” characterizes the immunological response. The discovery that some of the antibacterial and antiviral antibodies possess specific protective and curative capacities, presented additional evidence that the formation of antibodies has a teleological significance.

Later on, however, it has been revealed that under certain conditions antibodies are produced not only against pathogenic micro-organisms and their products, such as toxins, but also against a great variety of completely atoxic proteins and polysaccharides. As it is well known simple chemicals, which have an ability to combine with proteins in vitro or in vivo, form complex antigens and these induce the production of antibodies, the specificity of which is determined by the chemical (16, 19 a, 20, 38, 39, 77 a, 78, 88, 95, 111, 112). Naturally, it is quite difficult to claim that such antibodies have a protective or any other useful function. Experience has also shown that in the presence of such antibodies the responsiveness of the organism to the inciting antigen is so altered that a renewed contact with it elicits peculiar local and/or general reactions. This state of specifically altered reactivity has been originally named allergy by Cl. v. Pirquet and B. Schick, v. Pirquet and Schick at the same time also recognized in the course of acute and chronic infectious diseases various allergic symptoms, which are not caused by any direct action of the pathogen but are expressions of the specific change of the responsiveness of the host. The specific immunological response plays a decisive role
in the defense against infection. At the same time the immunological mechanisms may affect the host, causing structural and functional alterations, which can lead to disease and death.

According to the early teleological view of the protective role of antibodies, it was generally accepted that only substances foreign to the organism and the species of the host can be antigenic. This view had to be modified. Under certain circumstances some constituents of the host’s own organism can induce antibody-formation, and the antibodies so produced can in some way alter or damage the antigenic tissue system of the responding individual itself (6, 7, 8, 9, 16, 19, 54, 55, 56, 62, 67, 71a, 107, 107a, 115, 131, 132, 133, 135, 138, 150, 156, 168, 169). Body constituents exchanged between genetically different individuals of the same species can also induce immunological responses (3, 8, 10, 12a, 13, 16, 67, 125, 130, 135, 154, 171). These latter immunological responses may not involve the formation of free plasma antibodies. However, according to P. B. Medawar (112a) “antibody formation is a tyrannical concept, and the hunt for antibodies has caused us to neglect other important strategies of defence”. Certainly, there are other “tyrannical” concepts too, and it may be necessary to reinvestigate some trends and results in the field of allergy with regard to the above mentioned and other recent observations.

It is generally accepted that allergic reactions fall into two main categories; the immediate (anaphylactic, atopic) and the delayed (bacterial, tuberculin, eczematous) responses (5, 16, 19a, 20, 21, 23, 24, 88, 95, 111, 112, 112a, 123a, 125, 151, 152, 153). The controversial matter concerning the differences between these two types of allergic reactivity and the close bonds which unite them, will not be discussed here. I refer to the Introduction to the preceding volume of this series (88) and to M. W. Chase (19 a, 20, 21), W. J. Kuhns (93, 94, 95), H. S. Lawrance (97, 98), R. L. Mayer (111, 112) and S. Raffel (125a, b). Important contributions to the understanding of these problems are given in the present volume by S. V. Boyden, L. Brent, Ovary and B. H. Waksman.

According to the literature the immediate type of allergic reactivity is characterized by the presence of circulating (free) antibodies (anaphylactic and atopic or skin sensitizing antibodies [reagins]) whilst such antibodies cannot be demonstrated in allergic conditions belonging to the delayed type. These observations led to
the quite generally accepted conclusion that these plasma antibodies are “involved” in the immediate allergic reactions. It seems to me that this conclusion is not based on sufficient evidence. The presence of free antibodies in the serum of anaphylactic animals or allergic individuals can be demonstrated either in vivo by homologous passive transfer (C. Prausnitz, 123 a) or in vitro by means of various serological methods. The passive transfer of antibodies to normal individuals of the same species renders the recipient locally or systemically reactive to the specific antigen (123 a, 154a). The transferred antibodies must, however, become fixed to certain tissues (cells) before they can mediate an allergic reaction. Neither in anaphylactic animals, nor in allergic individuals is there any parallelism or connection whatsoever between the antibody content of the blood and local or systemic reactivity. Allergic reactions occur at the cellular site of the antibodies (or, in inverse anaphylaxis, on the cellular site of the antigen).

In vitro, uniform and reliable results can only be obtained by means of an indirect method, the neutralization technique. Anaphylactic antibodies or reagins, when mixed in optimal proportions with their specific antigen become firmly attached to it. At the same time both components lose their in vivo activity, since the antibodies cannot any longer transfer reactivity and the antigen is not able to elicit local or systemic reactions. Consequently, the antibodies as well as the antigen are “neutralized”*. Naturally, the neutralizing capacity of the antibodies cannot play any role in the eliciting of anaphylactic or allergic reactions. On the contrary,

* A similar method has been described in 1937 by V. W. Lippard and W. M. Schmidt [Amer. J. Dis. Child. 54: 777 (1937)].

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we have to consider that minute amounts of antigen do elicit severe local and/or systemic reactions in spite of the presence of an excess of “neutralizing” antibodies in the blood.* These facts, widely known and amply confirmed, cannot any longer be neglected. It must be clearly stated and always considered that we have no evidence whatsoever that the presence of free antibodies in the blood is a pre-requisite of the immediate type of allergic reactivity. The evanescent allergic responses are mediated by cell bound antibodies. There is no difference in this respect between the two categories of allergic reactivity.
As Z• Ovary points out in the present volume there is, however, some evidence that circulating antibodies are responsible for the Arthus phenomenon. This problem is not definitely settled (81, 148). Recently L. A. Sternberger (145, 146, 147) showed that large amounts of soluble antigen-antibody complex exist in the blood of rabbits, sensitized with bovine gamma-globulin. According to Sternberger the antigen originally injected “is rapidly degraded, but there persists in circulation a material which is structurally slightly different from the original antigen”. “This material does not react any more with precipitating antibody, but it is capable of reacting with nonprecipitating antibody and it might partake in some reactions of hypersensitivity”. This “modified antigen” is either a breakdown product of the original antigen or “a new material formed by the host in the response to the antigen injected”. The persistence of this material in the circulation may be of importance for the continued production of antibody. According to a preliminary report (“Medical News”, May 6, 1957) F. J. Dixon has shown in rabbits that the lesions of experimental serum sickness are caused by the trapping of soluble antigen-antibody complexes from the circulation. Undoubtedly, these observations open interesting new avenues for future research.

Immediate reactivity can be transferred by free antibodies. We have as yet no convincing evidence that the transferred antibodies are simply taken up by or attached to cells of the recipient, which then become reactive. There remains at least a slight possibility of some structural alteration or transformation of the antibodies in connection with this process. Consequently, it is not absolutely certain that free and fixed antibodies are entirely identical, in spite of their specific affinity to the antigen. The anaphylactic state in animals and the immediate reactive state in allergic individuals have the same mechanism. There are some differences between the functional (for instance precipitating, complement fixing) and physical (for instance thermostability) behaviour of anaphylactic antibodies on the one side and reagins on the other (95, 123 a). These are, however, not fundamental and

* This applies also to the “blocking antibodies” in the blood of specifically treated (desensitized) allergic individuals. “If the blocking antibody is the protective factor - and it may well be - the fact still remains to be proved” [W. B. Sherman, J. Allergy 28: 62 (1957)].

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are dependent on the species of the host, the nature of antigen and the history of sensitization (88, 95, 123 a). It has been claimed
that in contrast to anaphylactic or precipitating antibodies, which are confined to the y-globulin fraction of the serum, reagins belong to the /3-globulin fraction. W. J. Kuhns (95) showed, however, by means of zone electrophoresis on starch, that reagins against several antigens are found in the y-globulin fraction. Recently J. H. Humphrey and R. R. Porter (82) re-investigated this problem by means of chromatography of serum proteins on diethyl amino ethyl-cellulose and subsequent paper electrophoresis. These excellent investigations on eight reaginic sera confirmed Kuhns’ (95) results that reagins against several allergens “are found chiefly in the y1-globulins”. Furthermore, it has been shown that with the method used, the y-globulin can be resolved into four components. “The reagin content of serum from allergic subjects is almost confined to one of these components, which contains about 10% of the total y-globulin”. The serum from a person who was “very sensitive” to horse serum, gave a somewhat different result. “The reagin content appeared to be much higher ... and the activity more widely distributed” in the whole globulin fraction. Humphrey and Porter (82) seem inclined to suppose that “different cell types perhaps localized in certain tissues produce distinct kinds of y-globulin”. Here again different factors, such as the history of sensitization, play a more or less decisive role. Earlier findings by Porter and Humphrey (quoted from W. J. Kuhns, 95) indicate that during the sensitization of rabbits with different antigens (such as ovalbumin, type III pneumococci and influenza virus) the first series of injections induces the formation of antibodies which are confined to a slower moving fraction of y-globulin. Later on another, faster moving, antibody fraction occurs. The important work of A. M. Pappenheimer, Jr. and his collaborators (93, 94, 95, 97, 98, 120, 151, 152, 153) led to similar conclusions. J. H. Humphrey and R. R. Porter (82) tested their reaginic sera and the purified reagins for precipitins, but none were detectable. The study of the serological properties of different kinds of antibodies and antigens (allergens) is a very important field indeed. In an attempt to clarify the complicated interrelations between these extremely complex biological products, ingenious new methods have been developed. Ö. Ouchterlony1 s paper in the present volume on immunological analysis by gel-diffusion and gel-electrophoresis, gives an impressive and critical review of the important
technical progress made and the promising results already achieved in this recently opened branch of research. S. V. Boyden too, discusses in his review important serological methods, such as the Middlebrook-Dubos haemagglutination tests and the “coated tanned red cell technique” devised by himself (vide also 44, 143, 144).

Z- Ovary reviews the technique of the sensitive methods, developed by him in an attempt to demonstrate and measure antigen-antibody interactions in the skin of experimetal animals. An outstanding example of the usefulness of these techniques is the isolation of the allergenic fraction from horse-dandruff extract (D. R. Stanworth, 142a). The allergenic material is a single mucoprotein constituent containing 9% hexose in the form of galactose, mannose and glucosamine. Its molecular weight is about 34000. By gel-diffusion precipitin tests the presence of a small quantity of horse-serum albumin could be demonstrated in the dandruff material.

The skilful application of gel-diffusion and gel-electrophoresis in the immunological analysis of abnormalities in the human serum proteins by P. G. H. Gell (63) also led to important results. The great value of these new immunological methods, first and foremost the original Owcafer/oray-technique and its various modifications, for a “precise discrimination between similar proteins or high molecular-weight carbohydrates” is clearly demonstrated in the excellent papers by C. G. Pope (122b), W. H. Cole (24), J. Munoz (in 24) P. Grabar (67a), C. A. Williams, Jr. and P. Grabar (166), M. W. Wilson and B. H. Pringle (167) and L. Korngold and G. Leuwen (92a).

Serum proteins other than y-globulin are formed in the liver (65, 95, 160). y-globulins, such as antibodies, are produced by plasma cells. R. A. Good (65) states that it is now possible to “establish beyond reasonable doubt that the plasma cell is at least one source of antibody and y-globulin synthesis in experimental animals. Similarly y-globulin and antibody production in man have been associated with the activity of plasma cells”. In the Introduction to the preceding volume of this series (88) I discussed the sites of antibody synthesis. At present the accumulated evidence seems to support the view that the final stage of antibody synthesis is located within the plasma cells. Antibody synthesis is divided into two phases (29). According to F. Dixon et al. (29, 30, 31, 32,
the first phase of the antibody response is of short duration - a few hours - and probably represents “an initial period of adjustment of the host to antigen”. This phase takes place in radio- and cortisone-sensitive cells. Total body irradiation or cortisone treatment prior to the antigenic stimulation prevents this process and inhibits the antibody response. Strong evidence has been presented (10, 20, 21, 26, 36, 65, 66, 67, 73, 74, 75, 76, 77, 104, 117, 125, 129, 161, 164, 165) in support of the view that lymphocytes and/or “multipotent mesenchymal cells” are responsible for this initial adaptation phase of the antibody response.

The subsequent production phase (J. F. Dixon et al., i.e.) is effected by radio- and cortisone-resistant cells, chiefly plasma cells. During this phase antigen is eliminated at an increasing rate from the circulation and “with the elimination of all detectable antigen the level of free antibody rapidly attains maximum concentration, declining then at a logarithmic rate with a half life of five days, the same rate noted for the catabolism of homologous y-globulin” (29). As it is well known the course of antibody formation during the secondary (anamnestic) response to the antigen is different. The elimination of antigen is very rapid, free antibody appears considerably earlier and a relatively high circulating antibody level will be maintained over a much longer period. Thus, the secondary stimulation provokes a more powerful and prolonged antibody response (booster-effect). The important results of experiments dealing with the cellular transfer of circulating antibodies and the immediate type of allergic reactivity in experimental animals (88, 20, 21, 29, 30, 31, 32, 32a, 33, 34, 65, 73, 74, 75, 76, 77, 104, 117, 161) have amply corroborated these observations.

Antibody formation is apparently an alteration of “normal” y-globulin synthesis, which is the physiological function of the plasma cell system (65). Under the influence of the antigen some “biochemical lesion” (R. A. Peters, 122) occurs, and this results in a more or less lasting or permanent change in the y-globulin synthesizing enzyme system. According to F. M. Burnet (16) the adapted y-globulin synthesizer allows the formation of y-globulin molecules the surface pattern of which is complementary to that of the antigen. The theory of F. M. Burnet explains very well the specificity of antibodies, the nature of the secondary response and the formation of antibodies with various degrees of affinity to antigen. Antibody production after the elimination of the antigen
can be explained either by the self-replicating capacity of the enzymes involved or by the hereditary (cytoplasmic) transmission to the descendants of the plasma cells of the capacity to form antibodies. Furthermore, Burnet’s theory offers an explanation of the fact that the antibody forming system is apparently able to distinguish between material foreign to the reticulo-endothelial (phagocytic)-lymphatic-plasma cell-system (“not self”) and the constituents of the host’s own “expandable” cells or body fluids (“self”). “Self-components” which are antigens for other individuals of the same or different species are not antigenic for the host itself. Self-components and antigens are in general of the same chemical nature but possess different surface patterns. Embryos are not able to produce antibodies. This function appears Tn the early postnatal days. Burnet has also postulated that the self-recognition system develops during embryonic life and the early postnatal period. Any antigenic pattern, which reached the cell system concerned in this development, during this time, “would be accepted as ‘self’ and in subsequent life its re-entry into the body would not provoke antibody production”.

Recently J.V. K. Jerne (85) presented an interesting and stimulating explanation of antibody formation, the “natural selection theory”. According to him “globulin molecules are continuously synthesized in an enormous variety of different configurations”. Among them, by chance, there will exist molecules, the surface pattern of which is complementary to “any antigen to which the animal can respond”. In cases where the existence of such spontaneously aroused globulins can be demonstrated, we generally regard them as “natural antibodies”. If such natural antibodies are available at the moment when antigenic material enters the circulation they will combine with the antigen. The antigen antibody complex will then be rapidly eliminated from the circulation and, via the phagocytic and lymphatic system, reach the plasma cells, the sites of globulin synthesis. The plasma cells then tend to selectively and preferentially synthesize globulin molecules “identical to those introduced, i.e. specific antibodies”. If these are released into the circulation the same antigen will find a great number of complementary molecules at the second contact and the whole process will be repeated at a faster rate and to a greater extent. Thus, Jerne’s hypothesis explains the process of antibody formation without assuming enzymatic adaptation or any adaptive
change in the cellular mechanism of enzyme synthesis. The main point is the “selective and preferential reproduction” of an existing globulin pattern. According to Jerne “the globulin molecules that are eligible for preferential reproduction are those that can attach themselves to surface presented by the antigen before it is removed from the circulation.” This definition fits “natural” antibodies (globulin molecules which acquired specificity at random) as well as “specific antibodies” formed after antigenic stimulation. Jerne admits that “the postulate that the introduction of antibody molecules into appropriate cells can be the signal for the production of more of their kind” is quite an “unfamiliar” notion. According to Jerne “somewhere in the beginning”, i.e. during embryonic life, “globulin molecules of great variety of random specificities” are produced. All those having a complementary pattern to any antigenic material present at that time in the organism will be removed. Consequently when later on in early life “the much larger body of cells engaged in maintaining the composition of the circulating globulins by reproduction had started to function, the early removal of a specific fraction of molecules might lead to the permanent disappearance of this type of specificity”. In other words, the organism never has and cannot have “natural antibodies” complementary to “self-components” or other antigens present during embryonic life, and antibody production against them is thus impossible.

Turning to the group of delayed allergic responses I refer first and foremost to the contribution of S. V. Boyden in the present volume. The immunological response to antigens of the tubercle bacillus is a “classic example” of delayed allergic reactivity and has “interesting implications in relation to different kinds of antibody antigen reactions”. These processes are of basic importance for the understanding of the complicated underlying biological mechanisms.

According to S. Raffel (125a, b) immediate allergic reactivity may be established by the entrance of antigenic material into the organism, whilst the induction of delayed reactivity “requires the presence of entire infectious agents, or special conditions simulating their presence”. Under appropriate conditions antigenic material of all kinds is able to introduce both types of allergic reactivity. Immediate and delayed reactivity to the same antigen can be established and exist simultaneously. In ingenious experiments
R. L. Mayer (111, 112) recently disclosed the nature of the “special conditions” which determine the type of allergic reactivity. The type of the reactivity which will occur under the influence of a certain antigenic substance is dependent on the physical state of the antigen. Soluble, non-oriented, globular proteins induce immediate reactivity, oriented, fibroid proteins in se or as components of cells or micro-organisms elicit delayed reactivity. The route by which an antigen enters the organism is therefore, according to the results of R. L. Mayer, often a decisive factor in this respect. Antigens or haptens entering the organism combine with certain carriers. If antigenic material enters the organism via the skin it will be attached preferentially to “collagen, keratin or their precursors, both of which are fibroid and rigid proteins” and delayed allergic reactivity will occur. If the same antigenic material is introduced otherwise (injection, inhalation, ingestion) and has no access to fibroid protein but can be attached to soluble, non-oriented globular proteins - albumins or globulins - the resulting allergic reactivity will be of the immediate type. R. L. Mayer (112) assumes that since antibody is, according to the current theories, “complementary in form and shape to the antigen ... a complete antigen composed of a hapten plus globular protein carrier will produce antibodies which are different from those manufactured under the influence of complete antigens containing fibroid protein carriers. In the first case one may expect the formation of ‘globular’, soluble and therefore humoral antibodies, and in the second, the formation of ‘fibroid’ rigid, less soluble or insoluble, and therefore sessile antibodies”. Future research will have to decide the general significance of these important observations and stimulating conclusions. First and foremost it will be necessary to clarify the relationship between the results of R. L. Mayer (111, 112) and those of J. W. Uhr et al. (151, 152, 153). I also refer in this connection to St. Epstein (39), R. L. Baer (5, 6) and A. Rostenberg, Jr. (133a).

The antibodies which are responsible for the delayed type of allergic reactivity are not known. Delayed reactivity cannot be passively transferred by serum but only by viable or disrupted cells of the leukocytic series derived from the allergic organism (19a, 20, 65, 66, 67, 73, 74, 75, 76, 77, 84, 88, 95, 97, 98, 110, 111, 112, 117, 120, 133a, 151, 152, 153, 161, 164, 165). The nature
of the “transfer factor” present in the cells is unknown. In the delayed reactive state the specific antigen seems to exert a cytotoxic effect upon the cells of the allergic organism. This effect is demonstrable in vivo (for instance on the avascular cornea)* and in vitro upon explanted cells obtained from the allergic organism. The nature of this specific cytotoxicity and its connection with antibodies of any kind or with the transfer factor are unknown and the experimental data quite controversial. I refer to the reviews of S. V. Boyden, L. Brent, J. Ovary and B. H. Waksman in the present volume and to the stimulating papers by C. B. Favour (43) and H. S. Lawrance (97, 98).

Most important contributions to the solution of the problems discussed above emerge from studies of "the state of intolerance which is called into being by the transplantation of living tissues (homografts) between different individuals of the same species” (L. Brent). According to L. Brent, who together with P. B. Medawar and E. R. Billingham pioneered in this field, “evidence arising from the grafting of normal tissues and especially of skin leaves no doubt” that tissue transplantation immunity “is an actively acquired immunological response”. I refer to L. Brent's contribution to this volume. The reader is also referred to B. H. Waksman (present volume) and to G. H. Algire et al. (3), R. E. Billingham (12, 12a, 13), T. T. Odell, Jr. et al. (117a), B. O. Rogers (130), R. J. Scothorne (136), M. Simonsen (139a), G. A. Voisin and P. Maurer (154) and M. F. A. Woodruff (171, 172).

Tissue transplantation immunity is in many respects similar to the state of delayed allergic reactivity (97). Transplantation immunity can only be induced by intact tissue cells from genetically unrelated individuals of the same species. Such a skin-homograft for instance will be rejected after an initial “take” and a latent period of 10-14 days. The rejection of a second graft from the same donor is greatly accelerated, and is accompanied by severe inflammation similar to the delayed allergic response. Circulating antibodies cannot be demonstrated. The enhanced capacity to reject transplanted tissue is highly specific and can be transferred to normal animals of appropriate genetic constitution by cells

* Since this Introduction went to press S. SMossman and Ch. A. Stetson [J. Immunol.
presented evidence that “the corneal reaction of delayed hypersensitivity does not occur in an avascular tissue, and blood vessels may participate in this immunologic reaction as they do in others”. This is in full accordance with the view already expressed by P. Kallos and L. Kallás-Deffner in Acta med. scand. 109: 574 (1942).

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derived from the immune organism. The nature of the cellular transfer factor is unknown.
The finding of erythrocyte-mosaicism in bovine (R. D. Owen) and rarely also in human (J. Dunsford) twins led P. B. Medawar and his collaborators (112 a, b) to the discovery of acquired immunological tolerance. Animals injected during embryonic life or soon after birth with living homologous cells, accept in later life homografts from the cell-donor without any kind of immune response. These impressive results are in full accordance with the theoretical postulations of F. M. Burnet (16) and J.V. K. Jerne (85). As P. B. Medawar (112a, b) points out, immunological tolerance can be acquired for red-cell iso-antigens as well as for “isoantigens contained within living tissue cells and responsible for homograft reactions”. Red-cell iso-antigens are cytoplasmic substances and able to induce the production of humoral antibodies, belonging to the y-globulin-fraction of the plasma. The iso-antigens of tissue cells are constituents of the nuclei, and are not able to elicit the formation of free antibodies. “Immunity” against erythrocytes can be transferred passively by serum, immunity against tissue homografts only by “living immunologically activated cells” (Medawar) belonging to the leukocyte-series. It is important to note that tolerance can be acquired in an identical way in both cases. The presence of antigenic material “over the period of transition from the embryonic to the adult mode of response” (112a) specifically inhibits both types of immune response, the production of specific y-globulin as well as the mechanisms underlying the delayed allergic reactivity. This view resembles the concept of “serological maturation” (L. Hirszfeld, 1928). R. Hanan and J. Oyama (72a), B. Cinader and J. M. Dubert (21a), M. Cohn (22), and R. T. Smith and R. A. Bridges (139c) have recently shown that purified protein antigens are also able to elicit specific tolerance, when administered before the adult mode of immunological response develops. According to Medawar “tolerance represents a specific central failure of the mechanism of response”.

A spectacular discovery has recently been made by R. A. Good,
R. L. Varco and their associates (65, 66, 67). Good et al. could show that “transplantation of skin in both full and split thickness to two patients with congenital agammaglobulinemia resulted in prolonged and possibly permanent survival of the grafts. In one instance, the

successful ‘take’ has remained for 23 months. In the other it has remained 14 months”. Congenital agammaglobulinemia is a very rare disorder “featured by failure of gammaglobulin production and failure of immunological response to antigenic stimulation. The disorder appears to be an inborn error of metabolism generally transmitted as a sex-linked recessive trait occurring only in males”. This disorder has an acquired form too, which “may begin in either sex at any age and tends to be less complete than the congenital form of disease”. Both forms are associated with a functional disturbance of the mesenchyme which is “regularly reflected in failure of the development of plasma cells and pyroninophilic cells in response to primary, secondary, and tertiary antigenic stimulation”. Agammaglobulinemia involves a greatly enhanced susceptibility to extracellular bacterial infections, mostly caused by pneumococci, streptococci, meningococci, staphylococci or H. influenzae. According to Ch. M. Martin et al. (110a) a viral infection, serum hepatitis, is a major cause of death in agammaglobulinémie patients, and some mycotic infections, such as moniliasis, are quite frequent. It is at present generally accepted that the inability of agammaglobulinémie individuals to produce yglobulins and antibodies is the cause of their acceptance of homografts on the one side and their enhanced susceptibility to infections on the other. However, homograft rejection (transplantation immunity) has nothing whatsoever to do with y-globulins and humoral antibodies. Delayed allergic reactivity (bacterial allergy* and cutaneous contact sensitivity) occurs or can readily be induced in agammaglobulinémie individuals and can be passively transferred by their cells to normal recipients (65, 67, 95a 110a, 123). Thus, the acceptance of homografts can be caused neither by the insufficiency of antibody production, nor by an inability to develop delayed allergic reactivity.

Recent observations (in 52a, 65) show that immediate allergic reactivity, such as allergic (atopic) eczema, asthma and hay fever, also can occur in agammaglobulinémie individuals. We have three cases with acquired agammaglobulinemia under our observation,
all of them suffering from severe asthma and allergic rhinitis. According to R. A. Good (65) “one might be inclined to conclude that

* R. A. Good (65) points out, however, that “agammaglobulinémie patients lack sensitivity to streptococcal antigens to which the immunologically normal population possesses sensitivity in high frequency”.

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atopy can develop in the agammaglobulinémie person and thus be dissociated from classical immune response which is so completely defunct in these individuals. An observation in one of our cases calls this conclusion into question, however. One of our patients had had considerable trouble with hives and indigestion particularly following ingestion of fish products. Approximately eight years prior to study this patient developed agammaglobulinemia of the acquired type. Subsequent to the development of agammaglobulinemia the symptoms of atopy disappeared”. It is quite difficult to co-ordinate these conflicting observations. Agammaglobulinemia cannot be produced in experimental animals (G. L. Jordan, Jr., 85 a) and the frequency in humans is very low (65, 110a). The interpretation of the data available is, in my opinion, rendered more difficult by the “tyrannical concept of antibodies”. The physico-chemically quite homologous y-globulin fraction of the plasma represents a biologically heterologous population (53, 65, 82, 110a, 116a) and contains as well as antibodies molecules with different functions. One may perhaps speculate and assume that in the absence of certain kinds of y-globulin some cellular function cannot be performed, proceed with “normal” speed or reach normal efficacy. Agammaglobulinemia is an extremely grave disturbance of y-globulin metabolism, but even agammaglobulinémie subjects seem apparently to maintain some features of “biochemical individuality” (166a) and display differences in their reactions to bacterial or viral infections and to antigenic material. R. A. Good and R. L. Varco (66) point out that the deficiency of plasma cells in the hematopoietic centers - even after appropriate and intensive stimulation - represents the common denominator in cases of agammaglobulinemia. There occur, however, a great variety of other hematologic disturbances too, such as episodes of extreme leukocytosis or neutropenia, cyclic neutropenia, thymoma with absence of eosinophils, lymphopenia or absence of lymphocytes etc. One of our cases concerns a 34 year-old
woman with asthma, tuberculosis and anemia perniciosa (according to a personal communication from Dr. Good the first such case hitherto observed). The role of these hematologic disorders in agammaglobulinémie individuals is unknown. In cases of meyloma or lymphoma (65, 110 a) and in the rare cases of a chronic liver disease in young women (65, 110 a, 6 a) extreme hyper-y-globulinemia is a characteristic finding. However, these patients suffer at

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the same time from functional agammaglobulinemia. The y-globulin they produce is abnormal (see also J. Waldenstrom, 160) and their production of normal y-globulin is insufficient. Thus, the problems posed by the disturbances of y-globulin metabolism are not quantitative but are merely qualitative. We have under observation a group of asthmatics with normal y-globulin level in the blood, but suffering from frequent bronchial infections and subsequent exacerbation of the asthmatic status. Long-term y-globulin treatment (with doses far below those used in agammaglobulinémie individuals) in these cases has, in our opinion, a definite therapeutic value (unpublished observations). At the “Fifth Annual Symposium on Antibiotics” in October 1957 (preliminary report in “Medical News”, October 14, 1957) several instances were reported, where simultaneous y-globulin-antibiotic therapy were particularly helpful in stubborn cases where antibiotics failed (H. Welch). E.G. Knouf reported on nine children and one adult suffering from various bacterial infections (glomerulonephritis, bronchitis, rhinitis, staphylococcal meningitis). A wide variety of antibiotics failed in these cases, then a combination of y-globulin and chloramphenicol was tried. “There is little doubt that the effectiveness of chloramphenicol is augmented and the course of therapy shortened when adequate doses of y-globulin are combined with the antibiotic”. The effect was apparently dramatic in some cases, for instance in a three-yearold not agammaglobulinémie child, who suffered 21 attacks of croup and improved “remarkably” within 12 hours after receiving y-globulin. At the Annual Meeting of the American Public Health Association in November 1957 (preliminary report in “Medical News”, November 25, 1957) S. Sonea, A. G. Borduas and A. Frappier described “experiments showing that human y-globulin potentiates both penicillin and Oxytetracycline as antistaphylococcal agents. In experiments with mice Sonea et al. found that when y-globulin was added to the antibiotic regimen many of the animals withstood
challenges by usually lethal doses of staphylococci. Against strains resistant or partially resistant to penicillin y-globulin alone exerts a considerable protective effect. In such cases y-globulin probably have some kind of permissive effect.

An interesting approach to the rational solution of the therapeutic problem presented by agammaglobulinémie patients has been made by R. A. Good and associates (65, 66, 67) and by Ch. M. Martin et al. (110a). These workers transplanted lymph nodes from healthy normal donors to agammaglobulinémie patients. These homografts have been accepted by the recipients and it could be shown that the implanted lymphatic tissue produced quite large amounts of antibodies (y-globulin) on primary and secondary antigenic stimulation. At the same time large numbers of plasma cells occured in the transplanted tissue. Martin et al. chose typhoid H-antigen as a stimulus and could show that during the primary immune response approximately 6 mg. specific y-globulin per gram of transplanted tissue were released into the circulation every day. At the peak of the secondary response the daily production rate was 11 mg. y-globulin per gram transplanted tissue. Unfortunately, according to the most recent observations of E. R. Billingham and L. Brent (pag. 338 of this volume) “graft-versus-host reactions” can occur in such cases and they may have a deleterious effect upon the host (see also 139 a, 172).

Agammaglobulinemia is according to Good an “experiment of nature” and we are far from fully understanding its implications and significance. It seems to me, however, that the evidence available at present calls for a re-orientation of the antibody concept. J. H. Hanks remarked at a recent symposium (65) that “preoccupation with the stereochemical specificity of antigen antibody reactions seems to have diverted interest from the underlying, possibly strictly nutritional mechanisms” whereby cells may suddenly change their activities and their biochemical relations to the surrounding tissue and to the organism as a whole. Such a re-orientation has taken place in related fields of biology, such as host-parasite relationships (65), the mechanisms of microbial pathogenicity (80), and the resistance to toxic agents (137).

Ch. M. Martin et al. (110a) state that “agammaglobulinemia may fall in the category of iso-immune-diseases, akin to glomerulonephritis or rheumatic fever. There has been increasing evidence
in a number of parallel directions that animals can be induced
to make a wide variety of circulating and cellular antibodies
against their own tissues. The possibility exists that acquired agammaglobulinemia
may result from the manufacture of antibody
against one's own antibody producing system".
This hypothesis is purely speculative; I shall, however, use it
as a connecting link to the next group of problems discussed in
this volume (L. Brent, S. V. Boyden, B. H. Waksman, Z- Ovary),
that of cytotoxicity of antibodies as-a causative factor in heteroand
autoimmunologic diseases.

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As is well known experimental animals are able to produce
free antibodies against certain tissues from heterologous species.
When such anti-tissue-antibodies of heterologous origin are injected
into individuals of the organ-donor species they are trapped selectively
or preferentially in the tissue used to immunize the serumdonor.
These trapped antibodies apparently interfere with some
cellular mechanisms and alter the functional and anatomical state
of the tissue. Important papers in this field have recently been
published by W. F. Bale and I. L. Spar (7, 140), C. A. Basset et al. (8),
J. H. Baxter and H. C. Goodman (9), J. Freund et al. (54, 55, 56),
E. Witebsky and his associates (132, 133, 138, 168, 169), S. P. Halbert
et al. (71a), A. H. Coons (26a), and D. Pressman and L. Korngold
(124). In spite of extensive work it was not possible to find out
how cell-injury occurs under the influence of antibodies. Perhaps
antibodies have some direct effect on the cells. However, the possibility
cannot be excluded that the various alterations which sometimes
resemble human diseases, are caused by circulatory disturbances
or are secondary to other processes.
In the Introduction to the second volume of “Progress in
Allergy” (1949) I discussed the important investigations by E. A.
Kabat and his associates into experimental autoimmunologic encephalomyelitis.
Concerning autoimmunologic diseases the readers
are referred to recent reviews by A. Cavelti (19), and P. Miescher
(115) and to B. H. Waksman et al. (156, 157, 158), R. W. Luxton
et al. (107), I. M. Roitt et al. (131), J. Gear (62), I. R. Mackay et al.
(107a), and J. L. Tullis (150). Several important clinical and
pathological aspects are discussed in the following papers: 65,
52a, 92, 118a, 119, 128, 155, 159.
The most important group of autoimmunologic disorders, the
immunohematologic diseases, are thoroughly discussed in the present volume by B. H. Waksman. This discussion led him inevitably to the basic principles of allergy and to the basic problem, i.e. how cell injury and cell lysis is effected under the influence of antibodies or at least in connection with an allergic reaction. His review entirely covers this important field.

In all reactions which concern antigen and antibody, complement may also take part. In cell lysis or cell injury complement may have a decisive role. Complement, formerly a somewhat mysterious agent, once called by M. Heidelberger (79, 122 a) “immunity intensifier, diagnostic drudge and chemical curiosity” has been made more comprehensible due to the untiring research work of M. M. Mayer and his school. In my opinion, it is a great advantage to allergists, that M. M. Mayer presents his “Studies on the Mechanism of Hemolysis by Antibody and Complement” together with a complete review of the literature, in this volume of “Progress in Allergy”.

Perhaps it ought to be mentioned that a group of diseases, the collagene or mesenchymal diseases (52a, 65, 92, 110a, 118a, 119, 155, 159), such as rheumatic fever, systemic lupus erythematosus, polyarteritis, dermatomyositis, systemic scleroderma and thrombotic thrombocytopenic purpura, has also been connected with allergic or autoimmunologic processes (see B. H. Waksman). An interesting fact is that, according to R. A. Good (52 a, 65) and Ch. M. Martin et al. (110a), such diseases quite frequently occur in agammaglobulinémie individuals.

In the Introduction to the preceding volume of “Progress in Allergy” I presented experimental evidence that in guinea-pigs with experimental asthma the suppression of allergic processes by ACTH or cortisone can lead to parenchymatous lesions, chiefly endo- and pericardial warts of the type earlier described by E. Libman and B. Sacks as pathognomonic for systemic lupus erythematosus. Recently Ch. H. Slocumb, H. F. Polley, L. E. Ward and Ph. S. Hench (139 b) observed that during the course of long-term therapy with cortisone in a number of patients with rheumatoid arthritis, some signs and symptoms of systemic lupus erythematosus and/or periarteritis nodosa occurred. These findings are in full accordance with our experimental results. It is certainly important to remember that such lesions can occur and to avoid long-term treatment with
cortico-steroids in allergic cases. It may be pointed out once again (see also 88) that steroid therapy in these cases is no substitution therapy. In opposition to earlier results (40, 41) which are frequently quoted but entirely insignificant, recent investigations (139) have corroborated that there is no adrenocortical insufficiency in allergic individuals.

P. Kallós and L. Kallós-Deffner (90, 91) have recently discussed the pathogenesis of blood dyscrasias caused by drugs. Apparently, the etiology of a number of such cases lays neither in antibody formation nor in autoimmunologic processes but instead in inherited alterations of the biochemical structure of the cells concerned. An example of this is the glutathione instability of erythrocytes in

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male patients “sensitive” to therapeutic doses of Primaquine, discovered in the excellent investigations by E. Beutler and his team (11). This lability of sulfhydryl groups is related to glucose-6phosphate-dehydrogenase activity. A sex-linked gen of intermediate dominance is the causative genetic factor. The hemolytic anemia in such cases is not an auto-immunologic but rather a “molecular” disease (121, 42a). Pre-existing “biochemical lesions” (122) can possibly render cells more susceptible to non-specific noxious agents too. Such defects could under certain circumstances cause substances to enter the cell or attach themselves to it, thus altering its antigenic structure. Regarding the genetic control of response to antigenic stimuli readers are referred to the following papers: 37a, 130, 135, 149.

Since Sir Henry Dale started his “Adventures in Physiology, With Excursions into Autopharmacology” (28) by the study of the “Physiological Action of /?-Iminazolylethylamine” (histamine) in 1910 and by revealing “the resemblance of its actions to the main symptoms of the anaphylactic reaction in different species”, there is agreement that whatever else the allergic reaction may do to cells, it releases histamine from them. Histamine metabolism is a central problem in the field of allergy and the exhaustive review by W. Paton in the present volume elucidates its important and interesting implications and ramifications. Recent developments in this field, decisively promoted by W. Paton himself, added a great deal to our understanding of the functional pathology of allergic (and inflammatory) processes. The therapeutical application of these results, i.e. the use of antihistamine substances (27, 58, 72), is well
established and was exhaustively reviewed in 1949 in volume 2 of “Progress in Allergy” by R. Meier and K. Bucher and by P. Kallos and L. Kallós-Deffner. I also refer to the papers, presented at the Histamine-Symposium in London in 1956 (G. E. W. Wolstenholme and C. M. O’Connor, 170) and to the important papers by W. Feldberg and his associates (45, 46, 47, 141) and the excellent recent contributions by J. Lecomte (99, 100, 101, 102, 103), Th. Inderbitzin (83, 84), H. Westling (163) and R. S. Abernathy (1).

There is no doubt that histamine release is one of the most important consequences of cell stimulation or cell injury which is caused by or accompanies allergic reactions. The histamine so released exerts profound local and systemic pharmacologic effects. As is well known and generally accepted many of the local and systemic signs and symptoms of the immediate (and perhaps also of the delayed, 84) allergic reaction are mediated by histamine. It is of importance to point out that the mechanism by which the antigen antibody reaction releases histamine from cells is not entirely known. According to the results of the outstanding investigations by F. C. McIntire (109) plasma-proteases are not involved. McIntire found that “histamine is released from rabbit blood formed elements by certain simple chemicals of small molecular weight. Small changes in the chemical structure of the releasers produce inhibitors”. The results add to the evidence, presented by W. Paton, concerning the importance of the chemical histamine releasers. The effects of anaphylactic shock and of chemical histamine releasers have been compared by J. L. Mongar and H. O. Schild (116) and by E. A. Carr, Jr. and Ch. F. Curry (18). Histamine releasers of known chemical structure release under certain conditions histamine suddenly in all individuals of some species and in certain individuals of other species. (89) “Biochemical lesions” of some kind in certain individuals could be the pre-requisites of such occasional release of histamine by drugs, such as aspirin, or by certain foods (P. Kallbs, 89).

Some high molecular weight substances, such as dextran, are also histamine releasers in some species; so is anaphylatoxin according to the excellent papers by F. Hahn et al. (64, 69, 70, 71). According to the interesting observations of P. Meier et al. (113, 114) some bacterial polysaccharides possess remarkable antiallergic and antihistaminic activities.
Together with histamine other autopharmacologic substances are also released from various cells, such as mast cells (37, 68, 127), formed elements of the blood and tissue cells, and from serum (M. E. Mackay et al. 108). In certain species some polypeptides (J. H. Gaddum, 59) and serotonin (5-hydroxytryptamine) also partake in the allergic reaction. Serotonin (2, 15, 35, 42, 60, 96, 118, 126) is released in connection with anaphylactic (M. A. Fink et al., 48, 49, 50; P. Kalios and L. Kallós-Deffner, 91a) and anaphylactoid (D. A. Rowley and E. P. Benditt, 134; G. B. West, 162) reactions in mice and rats. T. P. Waalkes, H. Weissbach, J. Bozicewich and S. Udenfriend (see 91a) showed recently in an excellent series of experiments that during a systemic anaphylactic reaction in rabbits quite large amounts of histamine and serotonin are released (probably from thrombocytes) and appear in the plasma.

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Thus, the intensive study of autopharmacology added much to our understanding of the mechanisms of the allergic reaction. However, the important results achieved, show no complete solution to the riddle of allergy.

The famous American writer Carl Sandburg relates the following anecdote in his book “The People, Yes”:
“The white man drew a small circle in the sand and told the red man, ‘This is what the Indian knows’, and drawing a big circle around the small one, ‘This is what the white man knows’. The Indian took the stick and swept an immense ring around both circles: ‘This is where the white man and the red man know nothing’.”

This, I feel, quite truly describes our position. Here we are, red men and white men, allergists, immunologists, pathologists and clinicians; the more we try to widen the “big circle”, the wider seems the “immense ring” of our unsolved problems.

Finally, I wish to express my deep appreciation to all Contributors for their splendid co-operation. To Dr. Dr. h. c. Heinz Karger (S. Karger Medical Publishers, Inc., Basel and New York) I offer my sincerest thanks for his generosity and never failing friendship.
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