THE RELATIONSHIP OF AGE TO IMMUNOLOGICAL REACTIONS*

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The relations of heredity and environment to biological reactions have occupied a large place in most branches of biology and medicine, but it is only within comparatively recent years that they have been seriously considered in immunological studies. All elementary text-books contain statements regarding the effect of environmental or hereditary factors—racial, species, and individual immunities are postulated, and factors responsible for natural resistance are enumerated, but the subject has usually been disposed of in a few pages without any attempt at adequate explanation. It has most generally been supposed that the individual will react in a regular and almost predictable manner to a given stimulus, and that the immunologist may determine the nature of the response. But in more recent years, as the focus of attention, first directed by Pasteur upon the bacterium, swings back to that equally important factor, the host, new emphases are evident. The experimental epidemiological studies of Topley in England, of Neufeld in Germany, and of the Rockefeller group in America have proved the importance of an hereditary factor in racial resistance. The newer knowledge of nutrition has brought much interest in the effect of diet. Zingher's exhaustive diphtheria studies have thrown side-lights upon the effects of social and economic environment, and the studies of Huntington have proved that a climatic factor is of importance in general resistance.

The relation of the age of a subject to any one of his biological reactions is obviously of considerable interest. Yet in immunology, until recently, little has been done experimentally save to note the incidence of susceptibility to a given organism in various age groups.† Studies of this kind have revealed the well-known Schick and Dick susceptibility curves. The fact of a changing resistance with age is

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† Ssacharoff[209] has reviewed a lengthy bibliography on the susceptibilities of animals and man to various infectious diseases in relation to age.

so generally accepted, however, that even the layman speaks of the diseases of childhood, to which adults are immune by virtue of an accumulative immunizing process due to many subclinical, latent infections. That this is the classical view in immunology is without question. And that it shall remain an important principle in immunology is undoubtedly true, but it is more and more evident that certain other principles are being disclosed which also have a part in natural resistance. The newer investigations have revealed many interesting points, some of which are reviewed in the following pages. Only those relating to the generally accepted defense mechanism involved in antigen-antibody reactions are included, though obviously there are many other defense mechanisms of equal or greater importance.

About 1910, impetus to many age studies was given by von Dungern and Hirszfeld's[50] discovery of the inheritance of isoagglutinins. Ten years later Hirszfeld[90, 102, 103, 104, 105] postulated that all of the so-called "normal antibodies" are inherited structures, and he developed a theory of immunity in which the emphasis is placed upon the genetic constitution and the age of the individual concerned. This concept of a "constitutional serology" is founded upon the supposition that normal antibodies are biochemical organs which mature only at specific times in the history of the individual and result in a definite "serological maturity". Although endowed through inheritance with specific biochemical organs (antibodies), these will not react until serological maturity has been reached, at which time a fully developed biochemical reflex is supposedly active. To attempt immunization before this reflex is established would be as futile as to seek a response from any other reflex before it appears. This developmental process is called "serogenesis". The theory does not deny the influence of specific antigenic or of non-specific stimulation, but it assumes the constitutional nature of the individual to be the more important factor. A similar concept has been developed by Grasset[78], who speaks of a curve of aptitude to acquire immunity. This general view-point has recently received attention[52, 53] under various other names—"maturation panimmunity", "phylogenetic immunologic recapitulation", and "pubescent immunity". These ideas were founded upon the specific work of Hirszfeld and his coworkers and can be corroborated by interpretations from certain other lines of investigation which are so intimately concerned with the relation of age to

antibody formation that a review of them is desirable. In general, a consideration of the passive transfer of antibodies from the mother will be avoided.*

The Development of Isohemagglutinins

That in man the isohemagglutinins† develop with increasing age is well established. Soon after the discovery of these antibodies, Halban[88], von Decastello and Sturli[46], Langer[125], Schenk[195], and von Graf and von Zubrzycki[77] noted that the serum of the new-born exhibited weaker agglutinating ability than did the serum of adults. These antibodies were rarely present before the first month after birth, according to Happ[92], but they were always in evidence by the second year of life. The specific nature of the corpuscles, depending on antigenic constitution, appeared before that of the agglutinins. Many others have added confirmatory data.‡ Schiff and Mendlowicz[196] noted that in old age the titer of the isoagglutinins was lower and that there was a distinct variability in the titers at which the respective α and β agglutinins were to be found. In group O if the α agglutinin was strong, the β was strong also. This would indicate a kind of serological development or maturation in certain individuals. A characteristic quantitative curve of isoagglutinin titer was worked out by Thomsen and Kettel[218, 219] from data secured from 1400 individuals. This curve reached its peak with the 10-year age group and fell gradually through successive age groups. In persons aged 100 the value was as low as in infancy. Some individuals had high titers despite their age, indicating again an ability to produce antibody regardless of age. These authors also review the many papers dealing with the appearance of the A and AB receptors during fetal life. These receptors appear at

* In his monograph, *Chemical Embryology*, Needham[164] reviews this question of placental transfer.

† The term "isohemagglutinin" is undoubtedly the more correct designation for these antibodies. Usage, however, sanctions the use of the word "isoagglutinin," and herein the terms are employed as synonymous.

‡ Among these may be mentioned Cherry[36], Unger[230], Robertson, et al.[185], Hess[97], Dyke and Budge[51], McQuarrie[141], Biasi[21], Kirihara[113], Happ and Zeiler[93], Doelter[49], Ohnesorge[166], Lazarewicz and Zborowski[126], Rech and Woehlisch[179], Hara and Wakao[94], Hirszfeld[104], Debré and Hamburg[45], Morville[150], Mitchell[144, 145], Kemp[112], Knudtzon[120], Deilmann[47], Liedberg[129], and Thomsen and Kettel[219].

about the third month of fetal life, develop a maximum combining capacity at about the 15 to 20-year period, and show no decrease in old age.

Hemagglutinins and Hemolysins

There are many investigations on the natural occurrence of antibodies to antigens with which the individual cannot be supposed, under normal conditions, to have had sufficient contact to lead to an active process of immunization. In 1902 Halban and Landsteiner[89] studied sera from mothers and their new-born infants, finding lower values for agglutinin and less hemolysin for rabbit cells in the sera of the infants. A lack of hemolytic antibodies for various erythrocytes in fetal or infant blood of various animals, as reported by Schenk[195], Resinelli[181], Sachs[194], and Polano[178] soon confirmed this idea. An increase of amboceptors with age in horse and pig embryos was discovered by Rywosch[193], who also noted the sudden appearance of hemolysin for rabbit cells in chicks just after hatching. Quantitative estimations of complement and hemolysin in nurslings and some young animals in Moro's[148, 149] titrations again demonstrated that the sera of the new-born had much less hemolytic power than had those of adults, although breast-fed infants yielded sera with higher bactericidal power than did those artificially fed. The new-born infant of Bauer's[11, 12] experiments had no hemolysin for sheep cells. In examining human blood from fetal life to adulthood, Aschenheim[6] found a gradual increase in titer of normal hemolysin for sheep, ox, pig, horse, guinea pig, and pigeon erythrocytes. It is particularly interesting that he also demonstrated an increase in a specific antibody in successive titrations on one individual. In the same year (1909), Gewin[74] reported that he found no hemolysin for sheep cells and little for rabbit cells in the blood of 75 sucklings and 25 new-born children. Similar conclusions were reached by Bauer and Neumark[13], who studied the hemolysins for sheep, cow, guinea pig, and rabbit cells in 86 children. They noted that the breast-fed nurslings developed these amboceptors more slowly than did those artificially fed. Additional confirmatory data were contributed by Détré and Saint-Girons[48], who definitely stated that the younger the child, the lower the titer of hemolysin for rabbit cells. No sheep hemolysin was found in the sera of the new-born infants from the five families of Hirszfeld and Seydel's[106] careful study, even though this antibody was present in the parents, nor in the series studied by

Nattan-Larrier and associates[162] did any of the 77 fetal bloods have natural sheep hemolysin, although 67 of the mothers had this antibody.

Another group of investigators has studied the normal hemolysins demonstrable in various animal sera. Thus, in swine embryos hemolysins for sheep, goat, rabbit, and human erythrocytes could not be demonstrated by Sherman[204] until about the thirteenth week of gestation, while in chick embryos these antibodies appeared at about the time the chick was picking at the shell, and they increased with the age of the fowl[205]. Sordelli[208] reported that there was less hemolysin for sheep cells in young rabbits, and Bailey[9] noted the time of appearance in chicks of normal hemagglutinins active for the red cells of the guinea pig, rabbit, and rat. Those for the rabbit and rat appeared first (about the 16th day after hatching), and those for the guinea pig much later. Hirszfeld and Seydel[106] followed the development of sheep hemolysins during the growth of young rabbits, and later Friedberger and Gajzágó[68] concluded, from a study of 77 young animals from 15 mothers, that these antibodies first appeared after 75 days of life. In some animals the hemolysins might be present at birth, presumably transferred from the mother. These disappeared within 14 days. Maugeri[139] extended these studies to rats and domestic swine.

In 1929 Friedberger and Bock[66] and Friedberger, Bock, and Furstenheim[67] published the most complete work that has been done. They tested over 600 human sera for sheep hemolysin, and 300 for rabbit blood hemagglutinin, working out a normal antibody curve for man at various ages. Their results indicate that the titer rises until the 5 to 10-year group and falls definitely after 30 years. There was not a complete parallelism between the agglutinin and hemolysin content of an individual serum, and the correlation with blood groups was uncertain. Females had higher titers until 35 to 40 years of age. The blood of new-born children had no antibody, although 80 per cent of the mothers had hemolysin. In quantitative determinations the percentage of hemolysins rose from 21 per cent in the one-year group to over 88 per cent in the 20-year group and fell to 50 per cent in the 40-year group. In nine young and five old rabbits similar results were found. Analysis of Kagan's[110] recent titrations shows that a larger percentage of the sera from 360 children had agglutinins for sheep cells than of the sera from 410 adults. Quantitative titrations on 47 children and 22 adults showed high

titers less frequently in older individuals. Paul and Bunnell[171] examined 275 hospital patients and demonstrated a rapid rise in the sheep cell agglutinins of the serum during the first five years of life, reaching an irregular peak between five and fifteen, and then gradually declining with maturity and old age.

All of these studies with antibodies for various erythrocytes are of particular interest in connection with the concept of serological maturation, for in them the objection of an increasing active immunization arising from contact with the specific antigen is more easily ruled out, although the possible relation of heterophile antibodies, common antigenic patterns, etc. must be more thoroughly understood before the question can be settled, and the possibility of intestinal absorption must be duly considered. However, it must be admitted that some of these newer studies do challenge certain classical precepts of immunological teaching, and it may be well for both the old and the new to be subjected to the "grim logic of bacteriological forefathers"[242] before a final evaluation is made.

Other Normal Antibodies

Evidence suggestive of a development of antibodies with increasing age is found not only in hemolytic and hemagglutinating antibodies, but also in those specific for various infectious agents. Diphtheria antitoxin has been more widely studied than any other of these "normal" or "natural" antibodies. In 1895 Wassermann[233] concluded from statistical data that older individuals developed some specific protective power to diphtheritic infection. He proved the presence of protecting antibody in the sera of normal individuals ranging from 17 to 65 years of age, and though his group was small he suggested that there was an increase of this protective substance with age. Karasawa and Schick[111] demonstrated definitely that the presence of normal antitoxin varied from infancy to adulthood, and Hahn[87] supplemented this by showing that there is a drop in the antitoxin content in old age. But the most important work was that of von Groeer and Kassowitz[80, 81, 82], whose careful studies with the Roemer technic and Schick test gave a firm basis for the familiar Schick age-susceptibility curves which have been so exhaustively confirmed by Park, Zingher, and others. Whether this normal antitoxin is the result of accumulative active immunization processes following latent infections or whether it is to be explained on other

bases is still controversial. Andrewes, et al.[142] have presented a lucid review of the earlier evidence for and against the more generally accepted infective explanation, and a repetition of this evidence is unnecessary. More recently, Hirszfeld[98, 99, 100, 101] has correlated the presence or absence of diphtheria antitoxin (*i.e.*, Schick positiveness or negativeness) with blood group in a series of families and has suggested that the former was inherited and somewhat related to the latter. Snyder[207], Thomsen[217], and Rosling[190] have criticized Hirszfeld's results and interpretations on various grounds, but it is suggestive to note that Bay-Schmidt[15] and others have reported that although diphtheria is unknown in Alaska, Eskimos give a typical Schick susceptibility curve. Evidence of a similar nature has been disclosed by Sherwood, Nigg, and Baumgartner[206], who reported a high percentage of positive reactors to the Dick test among American Indian children of from 5 to 15 years of age (twice that of Zingher's New York percentage in a comparable environment) and a low percentage (about half of the Zingher figure) in those over 20. In view of the apparently high degree of natural immunity to scarlet fever enjoyed by the American Indian it is interesting to speculate whether this marked decrease in Dick positivity is a striking example of serological maturity or whether factors of local tissue immunity, racial or physiological differences account for it. Scarlet fever is also unknown among the Eskimos so it is significant that Heinbecker and Irvine-Jones[95] found no Dick positives in the 53 individuals of that race tested. Sera of three gave positive Schultz-Charlton blanching tests, proving the presence of antitoxin in those sera. The racial factor may be even more definitely indicated in the considerable difference, found by certain Oriental workers[5, 222], in the susceptibility to scarlet fever, as evidenced by the Dick test, between the Japanese and Chinese in Manchuria. The development of diphtheria and scarlet fever antitoxin might thus be interpreted as being dependent upon some innate mechanism of the individual and not alone upon the development of an immunity acquired through contact with the etiological agent.

A curve similar to the typical Dick and Schick curves has been recently presented by Bryce and Burnet[30]. They tested 316 individuals from birth to 78 years of age for the presence in their sera of an antihemolysin to the toxic lysin of hemolytic staphylococci. They have also divided their results into groups according to the quantity of antitoxin titrated in the sera. It is, perhaps, significant

to note that in the groups containing the larger amount of antitoxin there is not so great a tendency to show a drop in titer with increasing age. If the explanation given for the similar phenomenon observed in isohemagglutinins is applicable here, this is again the problem of the "strong reactor" and indicates a kind of serological development which is particularly marked in certain individuals. In studies upon rats they found that about 50 per cent had some staphylococcal antitoxin in their sera. These naturally immune rats responded immediately to a single injection of toxin with a sharp secondary type of response, while those animals lacking natural antitoxin showed only a delayed response after repeated injections. Again it would seem as though the presence of the natural antibody, possibly itself the result of a constitutional factor, influences the process of active immunization.

Turning to a consideration of other normal antibodies, many scattered observations may be found which confirm the fact of a deficiency of these bodies in early life, and their subsequent appearance in later years. In 1899 Kraus and Loew[121] failed to demonstrate agglutinins for *B. coli* in the sera of new-born guinea pigs although such antibodies were present in high concentration in older animals. In the same year Pfaundler[174] showed that with increasing age children yielded sera having an increase in the agglutinin titer for homologous coli strains. Another early worker to note a deficiency of antibodies in young animals was Jurewitsch[109]. He studied the agglutinins found for *E. typhi* in rabbits and guinea pigs and also tried, with no success, to produce an active immunity in the fetus by immunizing the mother. The young animals had few agglutinins but might acquire them soon after birth. If, however, these antibodies did not develop promptly, they did not seem to develop at all. Jurewitsch decided that the ability to produce agglutinins was an inheritable characteristic. A similar deficiency in agglutinins for *B. coli*, *B. proteus*, *E. typhi*, *B. typhi-murium*, several vibrios, and *P. suiseptica* was demonstrated by Mueller[152] and by Braun[28]. Bacteriolytic or bactericidal antibodies for *B. coli* did not appear in chick embryos until the 14th to 18th day of incubation in Rywosch's[193] studies. The deficiency of bactericidins for hemolytic *Staph. aureus* in the sera of new-born children can, according to Gutmann[86], be related to the CO_2 content of the blood. Fetal or infant blood was also thought by several groups of workers[127, 158, 188, 189] to be less bactericidal to trypanosomes. Weaker bacteriolytic or

agglutinative properties were also demonstrated in sera from new-born infants as compared with sera from their mothers by Schuhmacher[200], Halban and Landsteiner[89], Schenk[195], Klinoff[119], and Klieneberger[115]. This last author, applying a few absorption experiments with six strains of *B. coli*, found that the sera from new-born and adults exhibited different specificities to these strains. From this evidence he made the sweeping statement that serum from the adult differs quantitatively and qualitatively from that of the new-born, although he seemed not to realize the implications and significance of this declaration, nor to have collected enough evidence to prove his statement. The increase of agglutinins with advancing age was corroborated in guinea pigs for anticholera agglutinins and in horses for antidysentery agglutinins by Sordelli[208], and in man for antityphoid, Shiga, and X-19 bacilli agglutinins by Hirszfeld and Seydel[106]. These conclusions were made on the basis of comparative antibody content in groups of individuals of different ages. Gibson[75], however, was able to demonstrate in one litter of young rabbits a definite increase in the titer of agglutinins for *B. dysenteriae* "Y", *B. pyocyaneus*, and *Encap. pneumoniae* over an 85-day period. Very recently Blake[23] has determined the agglutinin titer to a non-type-specific pneumococcus in 690 individuals from birth to old age. The curve rose rapidly to a peak in early adulthood and fell again in old age. It was also the mirror image of the morbidity-rate curves for the various pneumococcal pneumonias. There is also an age factor concerned in the susceptibility of rats to pneumococci, according to the experiments of Ross[191] in which older animals were found to survive greater doses than did younger ones. This immunity differed with age, that for Type II appearing earlier.

The studies of Wright[237], Wright and Douglas[239, 240], Amberg[2], Bolaffio[25], and Much[151] indicated that there was little significant difference in the opsonic indices of infants and their mothers. Other investigators concluded that the opsonic index was definitely lower in sera of infants than in those of adults[31, 32, 35, 58, 220, 228, 229, 235]. Rabbit and guinea pig fetuses developed opsonin during the last third of intrauterine life (von Eisler and Sohma[55]). From one study including 72 infants, Wright[238] concluded that the opsonic index was often high after birth, was decreased for a time, and later increased. Amberg[2] presented data confirming this observation. There is little unanimity of opinion in the studies of opsonins at various ages, but the well-recognized unreliability of opsonic indices may well explain

the confusion. However, the differences in the reactivity of the phagocytic cells themselves may easily be an important factor, and there is considerable evidence that the cellular reaction varies sharply with age. Differences in the actual number of leukocytes may also be of importance. The experimental work on this subject has been reviewed by Ssacharoff[209].

The presence or absence of complement in the sera of the new-born has long been argued[159, 149, 139], and a summary of the reported findings has been given by Friedberger and Gurwitz[69] who, by Caesarean section in guinea pigs, showed that complement was developed in the last stages of fetal life and that, instead of conforming to the doctrine of serological maturation it remained constant throughout life[73]. Moore[147] and Hyde[107] have bred a strain of so-called "complement-free" guinea pigs,—sera from these animals contain no complement. This characteristic is definitely associated with a recessive Mendelian factor. It is obvious that the inheritance of this lytic principle gives some credence to Hirszfeld's idea that some heritable, constitutional factor plays a rôle in determining the capacity of an individual to acquire immunity.

The mechanism of the Wassermann reaction is still not clear. One of the more puzzling aspects of the problem is the fairly constant positive reaction obtained by the use of Wassermann antigens and sera of many normal animals—cat, dog, horse, mouse, etc. The humoral properties responsible for such fixation may be assumed to be antibodies of some sort. From our point of view it is significant that Mackie and Watson[136] were unable to demonstrate the reaction with sera from very young animals, and it is even more significant, from the point of view of establishing some basis for the idea of serological maturity, to note that these authors found that the power to fix complement, using a Wassermann lipoid antigen, developed in parallel with the increases in natural antibodies, such as antisheep hemolysin. Mackie and Fincklestein[135] found no reacting substances for many "pseudo-antigens", such as peptone, in the sera of young animals. In this connection the well-recognized lack of diagnostic significance of the negative Wassermann in the new-born should also be recalled.

The mere differences in susceptibilities of animals of various ages to lethal or spastic doses of various toxins may be indicative of differences in the normal antitoxic content of sera. Thus, von Behring[19] and Loewi and Meyer[132] reported that young rabbits were more

susceptible than were adults to tetanus toxin, although Kisskalt[114] could not demonstrate a difference in rats. He, however, failed to use very young animals. In experiments with diphtheria and scarlatinal toxin in guinea pigs and rabbits Beebe[18] was unable to demonstrate differences when the doses of toxin were calculated according to the body weight of the animals, as did Trask[223] in similar studies. But Beebe has emphasized that conclusions from these experiments are invalid until agreement is reached as to whether toxin should be given on the basis of body weight or of blood volume. Phisalix[175] stated that the m.l.d. of venom for dogs was less in young animals. A curious insusceptibility of young rabbits to scarlet fever streptococci was demonstrated by Parish and Okell[169], and corroborated by Trask[223], who felt that the low susceptibility was not due to the presence of antitoxin. Another interesting observation is that of Suzaki[214], who showed that dysentery toxin produces accelerated movements in the duodenum and jejunum of rabbits, more exaggerated in ten-day old rabbits than in adults. In this connection it may be well to raise the question of the panimmunity probably indicated in the poliomyeliticidal action of normal, adult, human serum as demonstrated by some workers[8, 202, 203]. Beebe[18] attempted to study the mechanism involved in the influence of age upon susceptibility to toxins. She tested the absorptive power of the liver, skin, and brain of rabbits and guinea pigs for diphtheria, scarlatinal, and tetanus toxins. No differences were demonstrated in animals of various ages, except in the case of brain tissue and tetanus toxin. With this tissue, particularly that from rabbits, there was a definite difference between week-old and adult rabbits in the removal of tetanus toxin from solution.

Thus, there is considerable evidence that the aging of the individual, with its accompanying physiological changes, may be a determining factor in the development of immune bodies.

Skin Reactions

The mechanism involved in the reactions of the skin to various antigenic and non-antigenic substances has yet to be determined, but there are scattered observations which bear upon the relation of age to antigen-antibody reactions. In 1907 von Pirquet[177] noticed that young nurslings often gave a negative intracutaneous tuberculin test even though at autopsy they revealed a well-developed tuberculosis.

Similar negative tuberculin tests in infants were reported by Bondy[26], Fischl[57], and Biberstein and Oschinsky[22]. The Dick and Schick reactions in nurslings have also been widely studied from this point of view. Von Groeer and Kassowitz[83] found that a fair percentage of infants, from birth to three months of age, reacted negatively to the Schick test, and Cooke and associates[42, 43], and Kuntz and Nobel[123] could elicit no skin reactions in some infants even when they injected large amounts of scarlet fever toxin. No specific antitoxin could be demonstrated by Cooke in the blood of these individuals. Later they might develop skin reactivity. These results were corroborated by Kuttner and Ratner[124] and by Paunsz and Cosma[172], who also injected toxin into such Dick antitoxin-free children and found a development of general symptoms but no exanthema. This lack of a dermal reaction in the presence of a systemic reaction in young individuals is in line with the work of Freund[62, 63] mentioned below. The skin sensitivity of rabbits to scarlatinal toxin increases with the age of the animal, according to Trask[223], whose rabbits were from six to twelve months old.

That skin reactivity and antibody of the tissues may vary independently was again suggested by the work of Tschertkow and Belgawskaja[226], who failed to demonstrate, in a series of nurslings, parallelism between the diphtheria antitoxin content of the blood and the sensitivity of the skin. Coca, Russell, and Baughman[37] observed a distinct difference in the reactions of guinea pigs of various ages to intradermal injections of diphtheria toxin, and Freund[62, 63], in careful studies of the tuberculin reaction in the same animal, came to the conclusion that although systemic hypersensitiveness was as fully developed in the younger animals as in adults, the dermal reaction was not. Similar conclusions are to be drawn from the work of Valtis[231] and Valtis and Saenz[232]. Two infants studied by Lesné and Dreyfus-Sée[128] and also examples of this lack of parallelism between skin and serum reactions. Sera from these infants failed to attenuate vaccinia virus injected into rabbits, and yet the babies gave negative cutaneous reactions until after they were three to four months old.

Many different organisms have been employed in skin tests described by various workers. Several of these indicate a difference in reaction in relation to age group. Using skin reactivity to a killed suspension of pneumococci, von Gutfeld and Nassau[85] demonstrated in 198 children an increase of from 17.5 per cent positive

reactors in the group under three months of age to 92 per cent positive reactors in the group of about one year of age. An insensitivity of the skin of nurslings and infants to injections of extract of *E. coli*, *E. typhi*, dysentery strains, and *Ps. æruginosa*, and to hemolytic and non-hemolytic streptococci was found by Tschertkow[225], Selter[201], and McKenzie and Hangar[140]. Negative skin reactions to askariden were noted in infants by Bruening[29]. Sutter[213] stated that the older the child the stronger the intradermal reaction to trichophytin A. Young rabbits subjected to subcutaneous injections of casein, horse serum, etc., gave no local skin reaction at the site of injection in Moll's[146] experiments, nor did they exhibit a definitely positive Arthus phenomenon in Freund's[64] studies, even if they had precipitin titers as high as 1:20,000. In another study Freund[65] found young and adult rabbits to react differently to intracutaneous injections of virulent pneumococci. In adults there was an extensive local inflammation and little bacteremia, whereas the young animals died of bacteremia.

It may be of importance to note that age is of significance in connection with the skin reactivity to substances of non-antigenic nature, for if the physiological changes consequent to increasing age are revealed under such circumstances it would seem that receptivity for, or reactivity to, antigenic agents might the more reasonably be expected as another aspect of maturity. Adelsberger[1] and Tachau[215] showed that young infants reacted negatively or but slightly to the injection of turpentine, iodoform, and other irritants into the skin. According to Adelsberger[1], positive reactions are more common in subjects more than two months of age. Friedberger and Heim[71] corroborated the negative skin reaction in ten new-born infants injected subcutaneously with eel serum or mustard oil. They also studied reactions in rabbits varying from 150 to 2000 grams in weight. The youngest animals gave negative reactions, and the authors gained the impression that in 900-gram animals the reactions were stronger than in the older ones. Thus, whatever the mechanisms responsible for skin reactions, there seems to be some factor which is definitely associated with the age of the individual concerned.

Active Immunization and Age

The production of antibodies following artificial stimulation would also seem to be somewhat dependent upon an age factor.

Evidence must necessarily be gleaned largely from chance reference, and there are many criticisms that can be made of individual experiments; few have been made for the purpose of evaluating the age factor. Studies attempting to prove or disprove the possibility of intra-uterine immunization of the fetus by active immunization of the mother absorbed the attention of Ehrlich and his students. These studies, reviewed at some length by Ssacharoff[209], are of little significance.

As early as 1897 Metchnikoff[143] stated that the ability to produce tetanus antitoxin was more highly developed in larger alligators. In 1904 Tschitschkine[227] fed ten six-day old rabbits with killed typhoid culture. There was little production of agglutinin and none of complement-fixing antibodies. In the same year Kreidl and Mandl[122] reported that they were able to produce hemolysins in the goat fetus. Bertarelli[20] fed killed typhoid culture in quantities based upon the weight, to young dogs, finding that animals 28 to 34 days old gave slightly higher titers than did older animals, and that the new-born gave low titers during the first days of life.

The transfer of unaltered protein through the intestinal wall to the circulation was a question of interest to the pediatricians of this period, and there appeared many studies dealing with the serum reactions of infants and young animals either naturally or artificially fed. Schkarin[197] could not demonstrate precipitins in the blood of ten young rabbits following subcutaneous injections of cow's milk until after the animals were 47 days old, and he noted that the artificially fed animals were even slower to develop precipitating antibodies. Ossinin[168] also believed that artificial nourishment retarded antibody production in infants, though in his studies both artificially and naturally fed infants were very slow to produce precipitins after the subcutaneous injection of cow's milk. Moll[146] found that three-week old rabbits produced much less precipitin than did adults. Three young rabbits exhibited only slight ability to elaborate bactericidins or agglutinins for the cholera vibrio. Subcutaneous injections of red blood cells in young animals resulted in the production of less hemolysin than in adults, but the young animals also seemed to have less local or general reaction following inoculation. In these studies differences in fibrinogen content, leukocytes, and other constituents were described in the blood of young and old animals. Wegelius[234] and Reyman[182] thought that the new-born goats in their experiments could be actively immunized

as easily as were the adults. In a study of anaphylaxis in guinea pigs Friedberger and Simmel[72] found that new-born animals actively sensitized to sheep serum were from eight to ten times less sensitive to the specific protein than were 200- to 300-gram animals. Inasmuch as young animals, passively sensitized, showed symptoms of anaphylactic shock in a degree only slightly less severe than adults, these authors concluded that there was an incomplete production of anaphylactic antibody in the young guinea pig. They reported similar results in young rabbits. Thomsen[216] also noted that the very young and the very old guinea pigs he had sensitized with serum were less sensitive than were adults, and the same conclusion was reached by Petroff and Stewart[173] with guinea pigs under 400 grams which had been sensitized to tuberculin by vaccination with killed bacilli. In 1914 von Groeer and Kassowitz[79], in a long review of immunity in the new-born, stated definitely that new-born animals responded less readily to active immunization. Frankenstein[61] immunized 20 nurslings to *B. typhosus* sera from three showed titers up to 1:100 for agglutinins and very few complement-fixing antibodies. Pastore[170], Bocchini[24], Auricchio[7], Schteingart and Cervini[198, 199] reported the presence of agglutinins in infants following injections of typhoid vaccine, but Corica[44] found no increase in opsonins. Bocchini[24], who used *B. typhosus*, *B. melitensis*, *Staph. aureus*, and *Staph. albus* vaccines found complement-fixing antibodies as well. It is particularly interesting to note that chickens in which Bailey[9] found that the hemagglutinins for guinea pig erythrocytes appeared normally 30 days after hatching would produce these antibodies 15 days earlier if stimulated by injections of homologous cells. Rohmer[186, 187] and Ribadeau-Dumas[183, 184] were unable to immunize actively very young and new-born infants to diphtheria with toxin-antitoxin mixtures or anatoxin, and Flood[59] found that young adults would develop diphtheria antitoxin faster and in greater quantity than would children of from five to ten years old. His studies also indicated that the amount of natural antitoxin present influenced the further development of antitoxin during active immunization. Young rabbits were successfully immunized by Nattan-Larrier and associates[160, 161] even though the young animals responded much less vigorously than did adults. Guinea pigs of various ages gave varying results in their anaphylactic experiments[163]. Of the 200 rabbits used by Gross[84] those under one year of age produced a titer of hemolytic amboceptor only about one-half as high as that produced

by older animals. Only occasionally did the rat fetus, as injected with guinea pig cells by Boucek[27] produce a 1:10 titer of agglutinin and hemolysin, but he did not believe his results to be conclusive. Grasset[78] was unable to confer any appreciable antitoxic immunity by injection of diphtheria anatoxin into fertilized eggs. However, if the antigen was administered in its toxic form the embryos were fatally sensitive. Kligler and Olitski[117] made a fairly systematic study of antibody formation in young animals. Guinea pigs under 300 grams and rats of about 20 to 40 grams in weight given subcutaneously injections of polyvalent typhoid vaccine responded less vigorously with the production of agglutinins and bactericidins. Trask et al.[224] found that during recovery from pneumonia the agglutinins for pneumococci were weaker in children than in adults, but that the protective bodies were the same.

The very careful work of Halber, Hirszfeld, and Mayzner[91] is particularly suggestive. They followed the development of the titer of isoagglutinins, antityphoid agglutinins, and partially of sheep hemolysins in 54 children from two weeks to five years of age who were being immunized to typhoid, diphtheria, or smallpox. Of the 30 children given typhoid injections three out of 20 children under one year of age reached an antityphoid agglutinin titer of 1:400 while all of the ten children aged from two to five years reached a 1:400 titer. The injection of typhoid vaccine stimulated, up to 800 per cent, the production of isohemagglutinins. If, however, no isoagglutinin had as yet developed in the individual, such heterologous stimulation, with one exception, was without influence. These facts are considered by the authors as very strong evidence for Hirszfeld's theory of serogenesis, which they conclude begins at the end of the first year. Following the administration of diphtheria anatoxin or smallpox vaccine similar increases in heterologous antibodies were found, though not as markedly as after the administration of typhoid vaccine. As before, the nurslings gave generally negative results and the older children often showed a 200 to 400 per cent increase of those antibodies already present. The response was always less in the younger, more "serologically immature" children. It is to be noted, however, that in 4 out of 54 cases, despite the presence of isoagglutinins, there was no increase of these antibodies upon the administration of heterologous antigens. In studies designed to evaluate the influence of age upon antibody formation in rabbits, Freund[64] definitely concluded that there was a weak ability to pro-

duce hemolysins for sheep erythrocytes, precipitins to horse serum, and agglutinins for *E. typhi* in young animals. His young rabbits were under four days of age at the time of inoculation. In Baumgartner's[14] studies rabbits between 50 and 70 days old developed about six times as much agglutinin to *B. enteritidis* in two successive series of immunizations as did animals about six months of age. In other words, at 50 days of age the animal produced a small amount of antibody, but by 70 days of age it had grown serologically much more mature and its ability to produce agglutinin was greatly increased. The adult animals, on the other hand, were serologically mature and responded vigorously upon the first inoculation. Although, as is to be expected, a second series of inoculations in these adults led to greater antibody production, the increase was not so great as in young animals which were maturing serologically during the period of immunization and were constantly able to produce more antibody. On the basis of microscopic examination of tissues from normergic and allergic guinea pigs of various ages Gerlach[73] decided that young animals were quite capable of producing antibody within the first month of life.

Another suggestive bit of evidence for a difference in the defensive reactions of young and old animals is found in the resistance which adult tissues offer to transplantation of heterologous neoplasms, a resistance which is not exhibited by embryonic tissues. Thus, the Jensen rat sarcoma, studied extensively by Murphy[153, 154, 155, 156] will grow in chick embryos but not in adult tissues. Sometimes even the addition of certain adult tissues seemed to inhibit the growth in the embryos[157]. Results with other transplantable tumors and other species have not been so clear-cut. Woglom[236] reviews very satisfactorily the literature in this field. The destruction of the foreign cells may not be due to any of the recognized immunological mechanisms, although it is probable, as Lumsden[134] has pointed out, that a cytotoxin of some sort is responsible.

Thus, there seems to be evidence indicating that very young animals have less of the so-called "normal" antibody and, compared with young adults, are relatively less able to produce antibody upon active immunization. If this premise be accepted, its explanation or significance is still forthcoming. Is it a question of a variable genetic factor working itself out in the definite maturation of a serological reflex, or is it merely the classical example of active immunization

through latent infection? The evidence from the literature which, in the main, supports the former interpretation has been presented in detail for the latter idea is so firmly entrenched that it is with difficulty that any other view can be approached.

Protagonists of the newer theory will have to contend not only with the traditional views on active immunization through subclinical infection, but with the newer problems of bacterial variation, common antigenic factors, and intestinal absorption. It seems, however, no admission of "intellectual recklessness"[242] to grant to both a rôle in determining the immunological status of the individual at any given age. The criticism recently hurled at the bacterial life-cycle enthusiasts by Zinsser[242] is no less valid, perhaps, for the serological maturity extremists. His statement that "either a proposition is demonstrable by experimentation and is confirmable, or it is not" is as concise a dictum for scientific investigation as we know. And yet, though the fact of a serological maturity cannot be said to be proved, there is apparently much sound experimental evidence to indicate that there are certain age factors at work and that these play some part in the immunizing process, a part which has not been considered by our classical school.

That such difference of antibody response at various ages is of any practical significance does not necessarily follow, for it is by no means suggested that antibody reactions are even factors of first importance in the relative susceptibility and immunity to certain diseases so common to definite age periods. But until other mechanisms which do explain natural resistance can be demonstrated, further investigations of antibody reactions are in order.

Qualitative Differences in Antisera from Animals of Various Ages

If the titer of two antisera be the same, the two sera are usually considered equivalent. That is, if by quantitative *in vitro* measurement the antiserum produced by one animal under one set of conditions is found to have the same value as another serum produced by another animal, the two sera are generally used interchangeably. There is abundant evidence that this inference is not strictly valid even though for practical purposes the supposition may hold. Thus the relation of Ehrlich units to the therapeutic effectiveness of diphtheria antitoxin has been disputed ever since Roux[192] first announced,

in 1900, that the two did not parallel each other. It is thus supposed by those who have followed Roux that there are certain qualitative properties of antibody which must also be taken into consideration in evaluating any antiserum. The avidity or speed of reaction between antibody and antigen is the quality most widely studied. That it differs in various antisera and also during the course of immunization of a given animal would seem to be fairly well established, even though not generally recognized. Barikine and Friese[10] and Baumgartner[14] have recently reviewed the literature. Baumgartner was also able to demonstrate in *B. enteritidis* agglutinating sera produced in rabbits of various ages a distinct variability in the avidity of the antibodies present. Antibody produced by young adult animals had a greater avidity than had that elaborated by very young animals and a slightly greater avidity than that produced by aged animals. These differences were quite independent of the titer of the sera, the amount of antigen administered, the mode of inoculation, and the length of the immunization period. Similar trends could be seen in agglutinins "freed" from serum proteins by the Olitski[167] method, and in the minor agglutinins of the sera, and also in hemolytic antisera. These observations indicate a qualitative difference in the antibodies produced at various ages, and so add to the idea of a quantitative serological maturity a new concept, that of a qualitative serological maturation process.

A qualitative difference in sera from old and young animals is certainly suggested in the work of Picado[176]. Two rabbits were injected for a period of 2½ months with human sera from 7 to 10-year old individuals and with sera from 62 to 76-year old individuals. The "young" antiserum precipitated better with a "young" antigen, and the "old" antisera with the "old" antigen. Complement fixation tests were unsatisfactory. He also injected three young rabbits with whole citrated blood of old rabbits. The antisera formed would not precipitate the blood of young rabbits but would react with the blood of the older animals. Assuredly this formation in young animals of antibodies reactive for old animals of the same species needs corroboration. Anderson and Rosenow[4] were unable to produce anaphylaxis in guinea pigs by repeated injections of homologous fetal serum. On the other hand, Lockeman and Thies[130, 131] were successful in sensitizing normal rabbits to fresh fetal rabbit blood.

Evidence from Clinical Statistics

The clinical literature abounds in evidence showing that age is a determining factor in susceptibility to disease. Statistical studies from the earliest times have been largely concerned with mortality and morbidity rates at various ages, and even the layman speaks of certain infectious diseases as children's diseases and so indicates how deeply the fundamental idea is ingrained into our thinking.

Of the great bulk of literature in the clinical field, the newer statistical studies are the most valuable for present purposes. Vital statistics are becoming more and more accurate, reporting is more and more complete, so that the later studies are of greater significance. It is not to be forgotten, however, that there is still much to be looked for before a given set of statistics can be taken as an accurate picture of the susceptibility or resistance in a given age group. Morbidity reports of State Boards of Health, school or private physicians, etc., usually fail to indicate the complete incidence of any disease and more particularly that of certain childhood diseases like chicken-pox or mumps, which are so easily overlooked. More and more it is realized that even many cases of scarlet fever pass unrecognized as such. Other factors are also at play. Important among these are: (1) the immunity derived from subclinical infections which may be active after the first few years of life, (2) the forgotten attacks of any disease, the percentage of which presumably will increase with the age of the individual reporting, (3) the effect of urban or rural life as shown by Fales[56] and Godfrey[76], (4) the relation of economic status so well brought out in Zingher's[241] diphtheria studies, (5) the result of irregular sampling as in the studies among various insured groups or in industrial plants, and (6) the prevalence of the particular disease under consideration.

However, within the past few years have appeared several excellent studies of the incidence of children's diseases in various American Communities which will serve to exemplify the type of evidence the statistician or clinician has to offer in the problem of the effect of age upon susceptibility. Ssacharoff[209] has reviewed many of the European studies. Though mortality and morbidity data are indicators of the comparative susceptibility or resistance in any age group, the morbidity figures seem to give the clearer picture. As early as 1916 Henderson[96] had taken a census of the contagious diseases of 8,786 children of London, Canada, and analyzed his data according

to the age of the child. In 1921, Collins[39] made a similar study of 6,130 school children in thirteen localities in Missouri, and in 1924 he enlarged his studies to a group of 31,353 children[40]. The excellent studies of Sydenstricker[210, 211, 212] in Hagerstown, Maryland, covered a smaller number of individuals, but the study was made by actual house-to-house visits over a period of 28 months, and covers many aspects of the problems arising in any morbidity study. In the same year Townsend[221], who was conducting an epidemiological study in various colleges for the United States Public Health Service, asked these students to report on the infectious diseases they had had in childhood. This personal method of reporting from an intelligent class of individuals also has certain advantages. Data from all of these studies and several other published and unpublished investigations have been collected in an excellent review by Collins[41]. The data have been subjected by him to rigid statistical analysis and the study constitutes probably the best work which has been done. The incidence of measles, whooping-cough, mumps, chicken-pox, scarlet fever, and diphtheria in white persons from birth to forty years of age are all considered in relation to previous history of the disease, death rates, and case fatalities at specific ages. The groups for each disease are from many communities and are as large as 20,000 to 50,000 each. The curves of incidence for the different diseases are similar, *i.e.*, they rise slowly to a peak somewhere in the first seven years of life and then fall rather abruptly. The maximum incidence in each disease varies considerably. Thus, diphtheria reaches its maximum at about three years of age and mumps not until seven. Eliminating those children already attacked by the disease in each age period, the proportion of the remaining children of different ages to suffer attacks of the diseases at a given age was computed. For every disease the maximum incidence among the children not formerly attacked comes at a later age than the same incidence among all children. The decline after the maximum is reached is not as rapid as in the instance of the rate among all children. Collins related the decline in any case to the development of an immunity and to changes in contacts.

From the field of experimental epidemiology have come studies in spontaneous and induced epidemics in laboratory animals corroborating the idea of increased susceptibility to certain organisms in some age periods. The observations on mouse typhoid by Amoss[3], and those of Kligler[116] on spontaneous epidemics of paratyphoid

among guinea pigs may be taken as typical. Again, Eguchi[54], Kligler and Rabinowitch[118], and Neufeld[165] found young animals more susceptible than old to amebic and trypanosomic infections.

Thus the greater susceptibility of the young to many infectious agents seems to be certain. On the other hand, it may be well to recall that there are many conditions in which the young show a relatively greater resistance than do the old. Typhus may be cited as a notable example. (See Fornet[60] and Martini[138].) The high survival rate in the young to CO, H_2, or CO_2 is also interesting (Reiss and Haurowitz[180]). The observation of Parish and Okell[169] on the relative insusceptibility of young rabbits to the streptococcus of scarlet fever is particularly worthy of note. Trask[223] has corroborated this observation and found the low susceptibility to be unaccompanied by the presence of antitoxin. In studies on the relative resistance of two inbred strains of mice to *B. enteritidis* infection, Loomis[133] found that a given dose was more fatal to animals of one and one-half to two years of age, than to those of six months to one year of age.

The Allergies

The experimental studies reviewed in the foregoing pages have been cited because of the evidence they may offer to the problem of a relationship between age and resistance. There is, however, a large field of study and observation which has not been considered and which, from many aspects, offers more interesting and conclusive evidence to the general problem under consideration than does any other type of immunological reaction. This is the field of hypersensitiveness. That age is a determining factor in various manifestations of the hypersensitive state is a fact so well recognized that clinicians use it as a determinant in diagnosis and the layman speaks casually of the manner in which he has "outgrown" this or that idiosyncrasy. Most of the conditions which are so conveniently grouped under the term "hypersensitiveness" are subject to the age factor, though it is to be observed that serum disease is a notable exception. Detailed discussion of the many observations is unnecessary, for it is enough to call to mind the history of many food idiosyncrasies and the age incidence in the asthmas and hay fever to realize the important relation of these conditions to the problem under consideration. Coca, Walzer, and Thommen[38] present an extensive bibliography.

Discussion

Thus, there may be accumulated a considerable amount of evidence that the young and adult differ markedly in the resistance offered to an invading microorganism. That at least a part of this may well be due to the quantitative and qualitative differences in the serological responses which have been demonstrated to be characteristic of animals of various ages also seems possible. It is by no means implied that this is an adequate or a complete explanation, and it is difficult to weigh the practical significance of the premises for which evidence has just been reviewed.

At the present time in every field of biological investigation the effect of the physiological age of the individual upon some body reaction is of primary interest. Step by step these studies reveal intricate mechanisms involved in a rebalancing of antagonistic hormone actions, in the development of basic reflexes, or in the complementary relationships of endocrine secretions during the life span of the normal individual. Each step gives new understanding to the differences which constitute the essential characteristics of youth, maturity, and old age. Perhaps, even more do these newer studies throw light upon those amazing differences found on either side of the hypothetical "normal" individual in the extremes of various pathological conditions and thus, in turn, make it possible to understand many of the individual differences found in persons of the same chronological age. For the age of the individual can no longer be defined in the simple terms of chronological years. He is much better understood if he be considered a mosaic of various ages. That he may be twenty-six years of age chronologically and only six years of age mentally is generally accepted. That he has other different physiological ages must also be apparent, as a certain sexual age, perhaps, and, as these studies just reviewed indicate, a certain serological or immunological age. Just as the balance of various endocrine secretions explains the physiological changes common to various age periods, so the hypothesis of a serological age may account for the changes in susceptibility to infectious agents common to various age periods.

Obviously many other factors associated with physiological age, aside from the serological ones, are bound up in any discussion of age and susceptibility or resistance. Histological changes in the skin or mucous membranes, which would lead to a break in those impor-

tant barriers of defense; anatomical alterations in the character of blood-vessels, lung parenchyma, or any internal organ; physiological fluctuations in the functioning of organs of internal secretion—all these easily enter into the picture of an increasing or decreasing resistance. For example, the observations of Becker[16, 17] and of Herlitz[96a] indicate a functional immaturity of the reticulo-endothelial system in new-born animals and infants of three or four months of age. But since the serological mechanism has been the dominant one in the explanation of defense toward certain invading micro-organisms, and since it is a fairly isolated reaction which lends itself to study under reasonably controllable conditions it seems particularly interesting to attempt to find in it some explanation of the changing resistance and susceptibility in different age periods.

If the ability of the individual to respond serologically varies with his age, might this not be responsible for his altered resistance to an invading organism? "Serological maturity" is a newly coined phrase, and, although the literature may reveal much evidence in its favor, it must finally be weighed in an assay taken to prove or disprove the truth of what it implies. It has been more generally supposed that the adult is able to resist the invaders to which he was prey in childhood by virtue of an accumulation of benefits from various latent infections. May he not also be aided by certain physiological changes concomitant with his increasing years and not related to his previous infections? These changes would allow the production of specific organs of defense, antibodies, which differ qualitatively and quantitatively from those produced in earlier life. The net result might be an increased resistance. Such a concept is given suggestive confirmation in the work of Jungeblut and Engle[108], who forced sexually immature, poliomyelitis-susceptible monkeys to precocious maturity with ovarian extracts and pituitary extract and found that they became insusceptible to routine intracerebral inoculations with the virus and that their sera neutralized virus in vitro. These are the aspects of serological maturity which are of interest to the immunologist and clinician of today.

It may be noted that not only in relation to specific defense mechanisms is this concept of a quantitative and qualitative serological maturity of interest. As an example of another kind of maturation process it enters the arena of general biology. The entire concept included in the term "immunity" is, after all, no more than a specific example of a consequence of a physiological response which

follows biological laws applicable in a realm much broader than that of infection. That it should follow a pattern of genesis similar to other biological reactions is not surprising.

The newer physiology seems to insist that the ability of the more highly developed organisms to maintain a constancy of their "internal environment" is one of great importance. This attitude, first assumed by Claude Bernard in his "milieu interne", is being developed by Cannon[33, 34] under the term "homeostasis". The relation of such a concept to the one of serological maturity just elaborated is challenging. Is the latter merely a result of other physiological changes, perhaps metabolic, endocrine, or nervous in character, which are tending to maintain homeostasis? Or, is serological maturity in itself a physiological change which in some way aids the maintenance of an internal constancy necessary to the well-being of the individual? These are questions which a much clearer understanding of the physiology of immunological reactions alone can answer. But the broad biological significance of qualitative and quantitative serological maturity must be acknowledged.

Summary

The problem of the relation of the age of the individual to the resistance he offers invading microorganisms is discussed from several aspects. The probable immunological factors at work in determining the differences found in young and old animals are particularly stressed. The concept of serological maturity,* *i.e.*, the development in the individual during early life of a certain biochemical reflex of antibody production, a development comparable, for example, to that of sexual maturity, is fully outlined and evidence for it gleaned from the experimental work of the past three decades. The young animal seems to have less of the so-called "normal" antibody than has the adult and also seems to be less able to respond to artificial antigenic stimulation than is the older animal. The antibody which is developed by the young animal may also

* The term "serological maturity" seems not to be entirely desirable. That it should be used for only one stage in the developmental process incorrectly designated "serogenesis" by Hirszfeld is obvious. The use of the terms serological infancy, adolescence, maturity, and senility is quite possible, though, perhaps, a bit ponderous. "Serological maturation" is suggested as a substitute, though the more familiar "serological maturity" has been used in this paper.

differ qualitatively from that elaborated by the adult. Clinical and statistical data as well bring evidence of the importance of age in determining resistance to certain invading microorganisms. That these observations shed some light upon the shifting susceptibilities to certain infectious diseases, epitomized, for example, in the term "children's diseases", is quite possible.

The preceding review and the following bibliography take no account of publications appearing after July, 1932.

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