INHERITED IMMUNITY*

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Immunology is a study of resistance to infection and presupposes interactions between host and parasite. How do the defensive forces of the host overcome the pathogenic powers of bacteria, viruses, and protozoa? By what methods can susceptibility be transformed into resistance, and how can resistance be increased? I am here concerned with one aspect of the problem—namely, the transfer of resistance from mother to offspring. This important subject has only recently received the attention it deserves, and many of its phenomena still await adequate investigation.

Immunity is often subdivided into (a) the innate, inborn, or genetic variety, which should probably be termed non-susceptibility rather than immunity; and (b) immunity proper, which is always induced in response to a specific stimulus either in the subject or in his mother. The passive transference from mother to offspring (congenital immunity) is either via the placenta (or in some animal species another form of intrauterine transmission) or via the colostrum and milk.

Innate Non-susceptibility

This variety of resistance to infection should be excluded from any discussion on immunity in the strictest sense, for there may be complete non-susceptibility without previous conflict or interaction between host and parasite; nevertheless, a brief survey is indicated on account of the emphasis in this lecture on factors of inheritance. Different animal species vary in their resistance to bacterial parasites and toxins. Thus, for example, man is resistant to canine distemper and rinderpest, and the dog and cat do not get measles, poliomyelitis, typhoid fever, and cholera. Sometimes the differences between species are not complete or absolute, as in the above instances, but partial or relative. The mouse is relatively insusceptible to diphtheria toxin—relatively, that is, to the susceptibility of the guinea-pig. The dog and goat are rarely infected with tetanus, and man seldom develops avian tuberculosis. The frog is unaffected by tetanus toxin in the cold, but succumbs on warming. The fowl is naturally immune to anthrax, but on exposure to a low temperature contracts the disease and dies. These observations draw attention to a complexity in this field—namely, that the participation of inheritance in the initiation of infection is sometimes obscured by other contributory factors (exposure to cold, malnutrition, fatigue, etc.) in an individual's environment.

Genetic differences in resistance within a breed or species certainly exist (Hill, 1934), and various aspects of this difficult subject have been widely studied. Among human beings, the relative racial immunity of, say, the white race to tuberculosis has received much attention; it may not, however, be the result of inheritance of an acquired characteristic, but rather a consequence of the elimination of susceptible persons for generations, with the result that the hardier survivors beget children less

susceptible to the disease. In the laboratory, selective breeding has been used to increase or lower the average resistance (to an infection) of a suitable strain of rats, mice, or other experimental animals. On the whole this work has not been very satisfactory, and there have been sources of error. Carriers may infect young animals, and thus influence their immunity state. In other experiments the results may have been vitiated by the passing on to some young animals of a temporary passive immunity, likely to mislead the unwary into the belief that a more resistant strain of animal was in process of development. Then again, as Hill, Hatswell, and Topley (1940) have shown, resistance may be acquired to one aspect of the attack of an organism—for example, the endotoxin of *Salm. typhi-murium*—without any increase in resistance to the one thing that really matters—namely, infection with the living bacillus.

Hereditary differences in the immunizability of guinea-pigs have been studied by Scheibel (1943), who was able to segregate a guinea-pig population, by selection and inbreeding, into a good strain and a poor strain of diphtheria antitoxin producers.

It is not surprising that we have not been able to influence to any extent the differences in susceptibility which exist between species or between individuals of the same species. We do not understand the mechanism at work, which must surely be a prerequisite for success. Variations in genetic pattern have been suggested, and all would agree that for an animal to be susceptible there must be mutual affinity between parasitic products and the body cells. Bigger puts it very aptly: the key (the bacterial or other parasitic product) must fit the lock (the cell protoplasm).

Congenital Passive Immunity

Passive immunity of homologous type is transmitted from mother to offspring (a) in man, apes, and rodents predominantly via the placenta (or other intrauterine mechanism); and (b) in sheep, goats, cows, horses, and pigs via the colostrum, which may be rich in antibody and is absorbed rapidly by the newborn animal. The alimentary tract of the young animal has high absorptive power and no digestive ferments, and these factors may explain the success of immunization by ingestion in certain animal species when placental transmission of antibodies is absent or negligible. A few hours after the first feed the titre of the serum of the young animal may equal or exceed that of the mother.

The relative importance of the placenta and the colostrum in transmission was believed to be due to the number of layers of tissue between the maternal and foetal circulations. The following summary was compiled by Mason, Dalling, and Gordon (1930) from the data then available:

	Layers of Tissue Between Maternal and Foetal Circulation	Placental Transmission	Importance of Colostrum
Pig	5	—	+++
Ruminants ..	4	—	+++
Carnivores ..	2	±	++
Rodent, ape, man	1	+++	±

Since the 1939–45 war a number of papers on the transmission of antibodies in the horse have been published by French workers at the Pasteur Institute (see, for example, Lemétayer, Nicol, Girard, Corvazier, and Cheyroux, 1949).

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Brambell and various collaborators (1946-50) have been studying intensively the mechanism of immunization of the mammalian embryo; their results have a bearing on the current theory of placental permeability. First, working with the rabbit, they have shown by electrophoresis and the ultracentrifuge that albumin, alpha, beta, and gamma globulins, and fibrinogen are present in the yolk-sac fluid of seven- and eight-day embryos. The proportions of these plasma proteins are similar to those in the maternal plasma. Secondly, agglutinin for *Brucella abortus* passes freely from the mother into the yolk-sac cavity before the allanto-chorionic placenta is formed. This finding signifies that agglutinins can, and do, pass from mother to foetus by a route other than the allantochorionic placenta.

Brambell considers that the yolk-sac provides a possible route into the embryo for maternal globulins in other rodents also, but he makes the important additional point that in man it is precluded on morphological grounds from replacing placental transmission.

Protein Chemistry.—At this stage it is useful to consider the bearing of protein chemistry on immunity findings in certain of the animal species shown in the above table. On analysing human maternal and foetal plasmas by electrophoresis, Longworth, Curtis, and Pembroke (1945) found that the concentrations of total globulin were lower in the newborn than in the mother. There was, however, a relative and absolute increase in the gamma globulin in cord serum, an observation which can be correlated with the higher titres of certain antibodies in cord blood than in maternal blood. The gamma globulin is, of course, a main protein fraction containing antibacterial substances such as typhoid agglutinins, antibodies to the viruses of measles, mumps, influenza, and many other infections, and to some extent antitoxins.

When we compare the serum of man with that of ruminants we find that the gamma globulin is absent in the latter at birth, and so, in accordance with expectations, are various antibodies. However, as we have seen, ingestion of colostrum rapidly makes good the deficiency. There is more globulin in colostrum (including human) than in the later milk, and this is connected with the building-up in the colostrum of antibodies of all kinds. Before or immediately after birth the colostrum titres of antibodies approach or may be much greater than the serum titres of the mother. Later the colostrum and milk titres fall rapidly (Mason, Dalling, and Gordon, 1930; Sugg, 1935). Marrack (1947) has given a useful review of the literature of antibodies in milk.

The gamma globulin in the serum of different animal species shows a fall in the early weeks of life, until the level is lower than that of the same fraction in the mother; the data accord with the immunological evidence of falls in circulating antibodies during that period.

Transmission of Antigens.—If antigens could be transmitted from parent to offspring this would have a profound influence on immunity mechanisms. However, there is no clear evidence that the ordinary bacterial and virus antigens are ever transmitted either via the intact placenta or in the colostrum and milk. The Rh antigen which produces iso-immunization of the mother is believed to pass the placental barrier from foetus to mother on account of some local damage of the villi: the significance and consequences of this accident are discussed later.

Formation of Antibodies.—A predominant part in the production of immune globulins is played by the local lymph nodes. Fat and muscle are also of subsidiary importance—not necessarily the fat and muscle cells, but possibly the granulation tissue formed in these organs (Oakley, Warrack, and Batty, 1949). Burnet and Fenner (1949) have reviewed the mechanism of antibody synthesis from normal globulins.

Immunity to Various Infections and its Acquisition

As we have seen, the mechanism of placental transmission of antibodies is so efficient in man that the colostrum and milk play a negligible and subsidiary part. From the immunological side, breast-feeding is not apparently of fundamental importance to the human infant; there is no evidence that breast-fed babies are better protected against the exanthemata than are artificially fed infants.

The routes of transference of antibodies from mother to offspring having been considered, what is the immunity state of the young animal, and especially the human infant, to various infections?

Antitoxic Immunity

Diphtheria

In the human species, if homologous antitoxin is present in the mother's serum it is transferred to her offspring almost entirely via the placenta. Barr, Glenny, and Randall (1949) have made certain observations which should influence the practice of immunization. They began with a study of the "concentration of diphtheria antitoxin in cord blood and rate of loss in babies": a noteworthy finding was that the antitoxin content of cord blood was as a rule appreciably higher than that of the mother's blood taken during labour or after delivery. Secondly, interesting data were obtained about the rate of loss. They state: "There is a steady logarithmic rate of loss of antitoxin in babies which averages 13.9% per week, falling from an initial average value 36.9% below that of the cord blood. The average antitoxin content of the serum of babies 10 days old is half that of the cord blood; subsequently the babies lose half their antitoxin every 4½ weeks."

Vahlquist (1949) and Barr, Glenny, and Randall (1950) independently found that passive titres above a certain level caused serious interference with active immunization as carried out by them.

Barr, Glenny, and I (1951) have completed a survey of diphtheria antitoxin in the cord blood of infants in various towns; large differences have been detected, and it is obvious that the immunity state of very many adults in this country is dangerously low.

The active immunization of mothers during pregnancy is contraindicated when the course is given for the benefit of their offspring (Di Sant' Agnese, 1949; Barr, Glenny, and Randall, 1950), mainly because it enforces postponement of active immunization of infants for a variable number of months—possibly till the second year of life.

Further detailed consideration of such important subjects as (a) the optimum time for routine immunization of children; (b) diphtheria in the first year of life (many cases and local epidemics have been reported in neonatal and nursing infants); and (c) the effect of the practical disappearance of diphtheria in many areas on the passive protection of the newborn infant, would hardly be justified in the present limited survey. I have discussed the literature of certain aspects of these matters elsewhere (Parish, 1949). Two points arise, however—namely, the interesting "resistance" of the mucous membranes and skin of young babies, and, secondly, the state of development of the antibody-producing mechanism in early life.

The mucous membranes of the young infant seem to be more resistant to infection than are those of the

older subject, and this may be one factor in the lower incidence of diphtheria in babies. In many infants the Schick test is negative even when there is little antitoxin in the serum; moreover, when it is positive the reaction tends to be smaller than in older persons (Wright and Clark, 1946). (The term "anergy" has been given to the extreme form of lessened skin reactivity). It is not surprising that the evidence from Schick readings in the early months of life has often been misinterpreted.

The literature is conflicting about the state of development of the antibody-producing mechanism of the newborn infant. Many have held that it is not fully developed, so that, for example, the diphtheria antitoxin response in young infants is not as satisfactory as in older children. However, older children, like older horses, owing to the possible development of primary immunity from the stimuli of sub-infecting doses of toxigenic bacilli, would be expected to respond better than the very young. The responses of young infants may also be "blanketed" by antibody acquired passively from their mothers; when this is absent, infants' cells can and do respond well to specific stimuli (Vahlquist, 1949; Barr, Glenny, and Randall, 1950).

The passive antitoxin so far mentioned in this discussion has been homologous in type. As Hartley (1948) has shown, heterologous antitoxin given to animals or to women in the late stages of pregnancy behaves differently. Horse diphtheria antitoxin given to a woman for therapeutic purposes is *not* transferred to her infant, who may contract diphtheria from her and require independent treatment with antitoxin. After this observation, Hartley carried out experimental studies in pregnant guinea-pigs. Unconcentrated (native) guinea-pig antitoxin and guinea-pig antitoxin concentrated with ammonium sulphate passed through the placenta readily. Unconcentrated horse serum and horse serum concentrated with ammonium sulphate passed through the placenta less well than the homologous products. The really unexpected finding was that refined pepsin-treated antitoxin, homologous as well as heterologous, was recognized in the serum of the newborn young in only minimal concentrations or not at all. The explanation of this failure in transmission is not obvious. It is unrelated to the size of the molecule, since the antitoxic molecule of refined serum is about half that of untreated serum; theoretically, this should facilitate its passage through the placental barrier rather than act as an impediment.

Other Infections

Staphylococcal Infections.—Murray, Calman, and Lepine (1950) have estimated the concentration of antibody to staphylococcal α -haemolysin in blood samples from the mother during labour, the cord, and also the infant in the first day of life. As had been shown previously for diphtheria antitoxin, the titres of the cord blood and the infant's blood were in the great majority of cases higher than those of the mother's blood. Anti- α -haemolysin is only one of the antibodies to staphylococci. While a passive immunity to certain specific antigens (toxins) may be transferred, the immunity state which is inherited may be far from complete; the newborn infant tends to have a poor resistance to bacterial invasiveness. Staphylococcal skin lesions, sometimes in association with conjunctivitis, have often been reported in maternity hospitals and elsewhere. Everything possible should be done to prevent cross-infection. The maintenance of good nutrition of mothers during preg-

nancy is also important, as this will assist local tissue immunity to staphylococci and other bacteria.

Scarlet Fever.—The serum of newly born infants has similar blanching power to that of their parents, indicating that the antitoxic levels correspond. Another interesting observation is that the skin of the newborn is usually insensitive to Dick toxin in considerable doses; skin sensitivity appears later (Cooke, Keith, and Ermatinger, 1927; Cooke, Brinkerhoff, and Woods, 1928; Cooke, Ermatinger, and Brinkerhoff, 1928). A scarlet-fever rash is also extremely rare in young babies. The "anergy" observed with diphtheria toxin has thus been noted with haemolytic streptococcal toxin also.

Tetanus.—Natural antibody to tetanus does not occur. Therefore mothers as a rule have no circulating antitoxin in their serum to pass on to their offspring, and interference with active immunization by congenital antibodies is not a practical problem at the present time as it is in diphtheria. However, it is worth remembering that women who have served in the Forces and been actively immunized with tetanus toxoid may have considerable amounts of antitoxin in their serum even after many years. Further, women attending summer camps in the U.S.A. may receive a course of toxoid. The congenital antibodies which the infants of such mothers may receive via the placenta may cause difficulty when active immunization is attempted in the early years of life. Cooke and her associates (1948) studied 284 healthy infants between 1 and 14 months old, and found that the mechanism for the production of tetanus antitoxin was as well developed in the early months of life as later.

Gas Gangrene.—As Mason, Dalling, and Gordon (1930) have shown, antibodies to *Clostridium welchii* type B—the lamb dysentery bacillus—are transmitted to sheep via the colostrum. They have also shown that a similar mechanism of transmission is at work in the cow, bitch, and mare. It is now well established that lamb dysentery can be controlled in the field by active immunization of ewes. In the human species, *Cl. welchii* antitoxins would presumably be transmitted via the placenta in the same way as other antitoxins.

Antibacterial Immunity

Whooping-cough.—Antibodies such as agglutinins and complement-fixing substances are passed on from mother to child via the placenta. If a woman is immunized during the last three months of pregnancy, the cord blood serum contains antibodies, usually in somewhat lower amounts than the mother's serum (Adams, Kimball, and Adams, 1947). Antibodies are also present in the colostrum, but, as in the case of diphtheria and tetanus, their significance is probably negligible. Agglutinins, etc., are not a measure of protection against pertussis, although their development indicates an immunological response to a specific stimulus. That is all one can say, for unfortunately there is little evidence that immunity in the sense of lowered susceptibility is transferred from mother to offspring. Whooping-cough in the newborn has been described by Keizer (1948). The infection is well known to be dangerous in the first year of life; the younger the child the more are lung complications to be feared. Early active immunization is important, therefore, and fortunately it is a safe and practical procedure, though success is not possible in all infants (Waddell and L'Engle, 1946).

Tuberculosis.—No immunity appears to be inherited; on the contrary, the child is more susceptible than the adult, and the younger the patient the greater the risk of infection. According to Blacklock (1947), the source of infection in a series of 144 cases of tuberculous meningitis was the mother in 44%, the explanation of this high figure being the close contact during nursing, dressing, fondling, etc.

"White Scours" in Calves.—The diarrhoea of young calves is often associated with *Bact. coli*, and it has been shown that any antibodies present in the colostrum are transferred to the young. We have seen that active immunization of the ewe has been used to good purpose in the campaign against lamb dysentery. Unlike lamb dysentery, however, "white scours" cannot be controlled in practice by active immunization of the mother, owing to the variable antigenicity of different strains of *Bact. coli* (Lovell, 1950). It is to illustrate this type of difficulty that I have mentioned this common disease of veterinary importance.

Leprosy.—Some immunity may be carried over from parents to children. When it is lost there is a phase of increased susceptibility, when child contacts of the disease are more prone than adults to contract the infection.

Syphilis.—Unless the infection is virulent, signs of inherited syphilis may not be well developed before the third week. Complement-fixing antibodies have been studied. If the infant is apparently healthy, a positive Wassermann reaction does not necessarily imply that infection has been inherited. A negative reaction does not necessarily signify that the infant is safe; repeated serological tests are indicated (Macfarlane, 1950). In addition to complement-fixing antibodies, the evidence for a partial (and very uncertain) "antibacterial" immunity to syphilis in rabbits and man is discussed by Wilson and Miles (1946).

Antiviral Immunity

Smallpox.—Viral antibodies are said to be equally high in maternal and infant bloods. Unsuccessful vaccination in the newborn may be due partly to these antibodies and partly to the skin refractoriness or "anergy," which I have also mentioned in connexion with the Schick and Dick tests. Antibodies and "anergy" usually disappear in three to four months—an arbitrary period, as exact estimations are not practicable. It should be noted that "anergy" has nothing to do with immunity. The usual recommendation is that infants should be vaccinated at four to six months, except in the face of an epidemic, when vaccinations should be carried out irrespective of age.

Measles.—The risk to the infant depends entirely on whether the mother has had measles. If she has, a passive immunity may be assumed which lasts for, say, four to six months. In the very few instances in which there is no history of maternal measles full susceptibility of the offspring is likely, although cases of measles in infants under 6 months of age are actually very rare. Thereafter the disease enters on its most dangerous phase, most deaths occurring between the ages of 6 months and 3 years.

Poliomyelitis.—In connexion with this disease we should recall that cases which can be diagnosed clinically are only a small percentage of the total of persons infected with the prevalent type of virus. When mothers

have neutralizing antibodies to a virus of poliomyelitis in their serum, as they often have, the same amounts are said to be present in the serum of their children at birth. As with the antitoxins, antibodies to viruses are transient and "disappear when the child is between 6 months and 2 years of age" (*J. Amer. med. Ass.*, 1950, 142, 525). In spite of the confident statements of some writers, only preliminary investigations have so far been made, and much further epidemiological and laboratory work is indicated. Baskin, Soule, and Mills (1950) have reported two cases of poliomyelitis in the newborn, and discuss whether the illness in one of these cases developed after an incubation period of only three and a half days or resulted from an intrauterine infection. At all events it follows from both cases that newborn infants are not invariably immune to poliomyelitis.

Immunity to Protozoal Infection

Malaria.—Congenital malaria is occasionally encountered (Jones, 1950) and has aroused much interest (*British Medical Journal*, 1950, 2, 451). Jones had drawn attention to the notable contrast between (a) hyper-immune indigenous populations, among whom infection of the placenta is very common but congenital malaria very exceptional, and (b) relatively non-immune, non-indigenous persons, among whom infection of the placenta is very rare but congenital malaria relatively less rare. He suggests that, as immunity to malaria increases, infection of the placenta becomes more frequent; at the same time the infected placenta becomes a more efficient barrier to the transmission of parasites, and consequently the incidence of congenital malaria falls. Peel and van Hoof (1948) have suggested that the numerous phagocytes observed in the placentae of natives might be expected to impede placental transmission of the parasite; this suggestion harmonizes with Jones's views.

Congenital acquirement plays a part in conferring increased susceptibility or resistance to a number of micro-organisms and toxins other than those discussed, and also to carcinogenic chemicals; the infections dealt with above are a representative and important selection.

There are many contributory factors in an individual's environment which tend to obscure the participation of heredity. Our knowledge, particularly of innate non-susceptibility, is incomplete, and more is in fact known about the hereditary transmission of certain diseases through the agency of abnormal genes than about the factors that determine resistance.

The Transmission of Iso-agglutinins

Antibodies are not invariably beneficial, and their interaction with the corresponding antigens may cause disease or death of the foetus. One aspect of this problem is the transmission of Rh antibodies.

The mother of a child with erythroblastosis foetalis, or haemolytic disease of the newborn, is nearly always Rh-negative. The father and the child itself are Rh-positive. The mechanism by which the disease is produced appears to be that small quantities of foetal blood containing the Rh antigen escape through the placenta (which may show a local lesion of the villi) into the maternal circulation and produce iso-immunization of the mother. Antibodies are produced in her serum, which pass back into the foetal circulation.

Antigen-antibody reactions then take place between these antibodies and the Rh substance in the infant's red cells and possibly other tissue cells. This is one instance in which the permeability of the placenta to antibodies is certainly not a protective mechanism.

The disease may take various forms. Apart from intrauterine death, occurring usually during the last three months of pregnancy, and leading to stillbirths, infants born alive may show various degrees of anaemia and jaundice, consideration of which is outside the scope of this lecture. However, in view of the attention I have given to placental and colostral transmission of antibodies, the following observations are interesting and relevant.

The infant is not necessarily affected when Rh antibodies are present in the maternal serum.

The first child of a marriage is seldom affected unless the Rh-negative mother has received a transfusion of Rh-positive blood. With this exception, the disease rarely appears till the second or third pregnancy.

What part does colostrum and milk play in erythroblastosis, and is breast-feeding permissible? Rh antibodies can easily be demonstrated in the breast milk of mothers whose blood serum contains antibodies, and who have borne erythroblastotic babies. Although these antibodies are not readily destroyed in the stomach of infants, there is no evidence that they are readily absorbed into the blood stream (Cathie, 1947). The consensus of expert opinion at present is that infants with haemolytic disease need not be weaned because Rh antibodies are present in the maternal milk.

Iso-immunization of pregnancy, leading to jaundice or other manifestations of the syndrome of haemolytic disease, has been observed in horses, mules, and dogs, and further work is in progress (Coombs, 1950). Many problems still await elucidation, or are insufficiently understood—for example, the factors influencing the extent and rapidity of the haemolysis and the degree of jaundice resulting. The capacity for cell regeneration and the rate of haemolysis vary considerably from case to case and influence the degree of anaemia. Holman (1950) says: "Of the other variables which make the understanding of this disease difficult, the most interesting is the occasional variation from pregnancy to pregnancy where one sees infants with the same Rh gene subject to the same or more powerful antibodies, and yet the later pregnancy will sometimes be less severely affected."

In connexion with the A, B, and O blood groups, death of the embryo in very early pregnancy may be due to antigen-antibody interaction—yet another example of misadventure from the inheritance of antibodies.

Summary

Different animal species show an inborn racial immunity, or non-susceptibility, to various infecting agents.

Congenital immunity is acquired by the passive transfer of antibodies made in the mother to her offspring, either via the placenta (or other form of intrauterine transmission) or via the colostrum.

There is a correlation between the transfer of antibodies and that of gamma globulin.

Transference through the placenta, after passive-immunization of the mother, occurs more readily with homologous than with heterologous antitoxins.

It is widely held that the active responses of very young animals to injected antigens are relatively unsatisfactory owing to immaturity of the antibody-producing mechanism.

However, the young human infant responds well to an injection of diphtheria or tetanus toxoid, provided that the level of the corresponding antitoxin transferred from the actively immunized mother is so low as not to cause interference.

Congenital immunity to a representative variety of micro-organisms and toxins has been considered in the main sections of this lecture. In a concluding section, a brief account has been given of certain aspects of Rh-antigen-antibody interactions, and it is shown that the transmission of antibodies is not invariably beneficial.

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The *Manchester Guardian* reports that the Committee of Inquiry into Weights and Measures Legislation recommends that the Government should take steps, in co-operation with the Commonwealth and United States, to abolish the Imperial system of measurement in favour of the complete adoption of the metric system over a period of about twenty years. Sir Hartley Shawcross, in a written reply in the Commons, said that there were many difficulties, and pointed out that the Government was not in any way committed to adopting the recommendation.