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# Abnormal immune response in burns

J. KOHN
Med. Dip., D.C.P., F.R.C.Path.

*Department of Pathology, Westminster Hospital Teaching Group, Queen Mary's Hospital, Roehampton, S.W.15*

THE immune response to burns is a very complex phenomenon. It is influenced by a series of factors such as the extent and severity of burn, depth, age, presence or absence of infection, type of treatment, etc. The normal response is reflected by the level of the gammaglobulin, or strictly speaking by the levels of the immunoglobulins present in the serum of patients with burns. This applies to humoral immunity: we do not know much about the cellular type of immunity. There are also quite marked individual differences in the response.

In uncomplicated cases the initial response to thermal injury is a drop of the gammaglobulin which as a rule depends on the severity and the depth of the burn. All immunoglobulins show an initial fall, the lowest level being reached within about 48 hr after the burn. This is consistent with and parallel to the fall in the total protein values. The deeper the burn and the greater the area affected, the more pronounced the decrease of the gammaglobulins. The fall of the gammaglobulins lasts sometimes a few days and only slowly starts rising again within the next week or so. The further behaviour of the gammaglobulins and the values of the individual immunoglobulins will vary according to the case and whether or not infection becomes established. Changes of concentration result from interplay of synthesis, catabolism, leakage and redistribution between the burned area and intravascular space (Arturson, 1971). The immunoglobulin which is affected most is the IgG, the levels of which may fall well below 100 mg/100 ml or about 10% of the normal values. In some very severe burns, all of them with fatal outcome, the IgG fall was very profound indeed, between 60 and 140 mg/100 ml (Kohn & Cort, 1969). The low IgG level may persist for quite a long while. It may sometimes take a month or more before it starts rising and it may be 6 weeks before it reaches the pre-burn values. It is very difficult to correct this deficiency and even administration of relatively large volumes of plasma or gammaglobulin will not raise the IgG values to anywhere near normal levels. In the later stages there is sometimes quite a dramatic rise probably due to infection and figures well above average and above the pre-burn values are reached. In children the situation is similar as far as IgG is concerned, but there seems to be a more rapid return to normal. There are less dramatic rises of the IgG, but the initial fall in the first few days occurs and depends on the extent and severity of the burn.

The IgA usually shows an initial drop and in many cases there is a consistent rise over a matter of weeks to levels 200–300% above the base-level values obtained from blood samples taken as soon after the burn as possible, within a matter of the first few hours. This increase of the IgA values seems to be accentuated with age; in very small children it is not as marked.

IgM values show relatively little variation; the initial drop is not pronounced probably because the IgM is an intravascular immunoglobulin, which does not migrate freely through the vascular wall. Considerable rises, however, can be observed in infection, particularly of the Gram-negative type, possibly due to endotoxin response. The greater fall of the IgG compared with that of the IgA and particularly the IgM, has been confirmed by the studies of the immunoglobulin levels in blister fluid which showed that the serum : blister fluid ratio is about 1·2–1·4 : 1 for IgG as against 3–4 : 1 for the IgA (Kohn & Cort, 1969). The IgD levels show the greatest individual variations but an initial fall usually occurs and the levels of IgD return to normal in severe burns within 1 month. Usually there is a decrease of the IgE in the early stages, but in some cases a very marked increase of IgE was noted, up to tenfold of the original level. As an increase of IgE in the blister fluid was observed as well, local production of IgE in burns cannot be ruled out.

Formation of bacterial antibodies follows the colonization of the burned surface by various types of bacteria and subsequent infection of the burned skin, possibly involving the deeper layers. Bacterial antibodies can be found within approximately 2 weeks from the time of burn. The time when the first traces of bacterial antibodies appear will of course depend on a sufficient load of micro-organisms to provide an adequate antigenic stimulus. A considerable number and variety of bacterial antibodies have been demonstrated in burns. All types of antibodies

have been reported: precipitating antibodies (Kohn, 1964; Zivanovic, 1968), agglutinating antibodies, haemagglutinating antibodies, complement-fixing antibodies, heterophile antibodies (Kano, Milgrom & Rapaport, 1966) etc. Of course we do not know whether these antibodies demonstrated in the circulating blood stream have any protective function, most probably not. They may well be just an expression of antigenic stimulus being present. One possible reason why antibodies are so easily produced in burns and reach sometimes high titres could be the fact that the area where the bacterial colonization or infection occurs is covered with necrotic tissue and, of course, large numbers of dead micro-organisms are also present. This, it is suggested, may act as an adjuvant increasing the immunological response. This is only a hypothesis and we have no experimental proof for it. In severe burns, however, there is clear evidence of suppression of the immune response both in man and in experimental animals. A marked impairment of the RES activity in the shock phase following burns has also been reported (Lamperle, 1970). This is obviously very important and helps to explain the pattern of the 'burns disease'. I think one has to emphasize that there must be a certain minimum surface area of skin involved (about 20–30%) before any significant changes occur. There is in fact a good correlation between the body surface affected by the thermal injury and the degree of immunosuppression. This has been demonstrated following experimental inoculation in animals. Precipitin reactions against *Streptococcus pyogenes* for instance show a very definite fall correlated with the area of body surface affected. The same applies to other bacterial antigens which have been studied and used for immunization of experimental animals during various stages of the burn. This immunosuppression becomes prominent within about a week after the burn. Immunization of animals on the first day of the burn results in a much smaller degree of immunosuppression. The effect of the burn on the immune mechanism must take time. The defence mechanism in the first few days after the burn is probably not considerably impaired and may be capable of fending off infection. Unfortunately, however, the defences drop just when they are needed most, that is at the time when the infection becomes established, within a matter of a week or so. The period of immunosuppression may take quite a considerable time to return to normal. Judging from clinical rather than experimental evidence the situation seems to improve as soon as adequate skin cover is provided. Following early skin grafting, i.e. within a matter of a few days, the susceptibility to infection seems to be definitely diminished, and the incidence of serious infection in these patients is relatively small (Janzekovic, 1968). On the other hand, in patients in whom for one reason or another skin grafting had to be delayed, the risk of severe infection and septicaemia appears to be much greater. Experimental evidence is also available for the presence of suppression of delayed hypersensitivity reactions. Application of 20, 30 and 40% body surface area full-thickness burns markedly reduces or abolishes the ability of tuberculin-sensitive guinea pigs to exhibit delayed hypersensitivity skin responses to this antigen (Casson, Converse & Rapaport, 1967). This effect is noted within 24 hr after burning, reaches a maximum 2 weeks later, and persisted during the entire period of testing (5 weeks).

In another series of experiments, burned patients and control individuals were tested with a battery of antigens including streptokinase, streptodornase, tuberculin, mumps and diphtheria toxoid. Nearly all the control individuals responded to at least one of the antigens used. Only about 2% were anergic. These results were in sharp contrast with observations made in all the individuals with burns exceeding 30% body surface who were tested with the same antigens during a period extending from 10 days to 67 days after injury. All burned patients were anergic to the battery of antigens used at the first test. In patients with smaller areas of body surface affected the response was correspondingly less dramatic, but a definite diminution of the response was observed in nearly all the cases ranging from 5 into 25% body burn. The results of this study showed that delayed allergic responses are depressed in thermal injury and that the degree and relation of the effect are related to the severity and extent of the injury. These studies clearly indicate the importance of the cellular hypersensitivity mechanism in the control of bacterial infection. Similar observations were made with prolonged homograft survival in burned patients, which is another very important factor (Rapaport *et al.*, 1964).

There seems to be little doubt that in older patients the defence mechanism is grossly impaired. Studies carried out in our hospital correlating the incidence of infection with age show a direct relationship (Kohn, 1965). This could be particularly clearly demonstrated in cases where the body surface affected by thermal injury was between 30 and 40%. Within 3 weeks from the burn *Ps. aeruginosa* could be isolated from all patients over 50, but only in about 60% of patients under 50. The overall figures for the incidence of infection in patients with a body surface burn of over 10% were 46% for patients under 50 years old and 73% for patients over 50 years, the latter being nearly double, which is highly significant. Another study correlating the titres of antistreptolysin and anticoli in various age groups produced similar results, the anti-*Esch. coli* showing the largest and the antistreptolysin titres showing the

smallest differences. The two groups of patients studied were aged 15–30 years and 60–91 years. This is also reflected in the mortality figures, some of which undoubtedly related to infection. If one introduces 60 years as an arbitrary dividing line then the mortality of burns for body surface area above 40% in patients over 60 years of age is almost invariably 100%, whereas younger people have approximately a 50% chance. The figures are even more dramatic in smaller burns. The statistics of our burns unit for instance show that the mortality in cases with 10–19% body surface area is only about 2% in patients under 50 years, but it is just over 50% in patients over 60 years.

Four components of complement, the C1, C2, C3, and C4 have been studied in third degree burns (Arturson & Fjellstrom, 1966). A very profound drop in all four components was found in the first 3 days reaching a minimum at about the third day and then slowly rising but never reaching the baseline levels. The C3 and C4 showed a continuous drop without recovery. This may well indicate the presence of antigen–antibody complexes, which after all, has been postulated by quite a number of workers. Whether these are auto-immune phenomena is rather doubtful, the timing would be wrong.

C-reactive protein (CRP) was estimated at various stages of severe burns in our unit (Kohn, 1961). There was a definite relationship between the extent and severity of the burn and the titre of CRP. The first traces of CRP could be demonstrated about 8 hr after thermal injury. The titre then slowly rose within the next few days, first in the blood and only subsequently in the blister fluid. The presence of CRP can usually be demonstrated as long as there are still unhealed areas. Following complete recovery CRP disappears from the blood stream. Any intervening complications followed by further tissue breakdown were expressed in the rise of the titre of CRP. On a few occasions an unexplained pre-terminal drop of CRP was observed. This drop was very considerable and amounted to 1/20 of the value estimated the previous day.

A very interesting phenomenon, splitting of the IgG molecule in the circulating blood, was observed. On immunoelectrophoresis the IgG line shows a characteristic split similar to that observed after papain digestion. This enzymatic cleavage is also known to occur in sera which have been stored for a considerable period of time or which have been contaminated with micro-organisms. In burns, however, it can be demonstrated in fresh sera. This suggests that the enzymatic split is caused by some proteolytic enzyme circulating in the sera of burned patients. The most likely candidate would be plasmin.

We know relatively very little about the cellular immune response in burns and this is a subject which is well worth studying and may well bring a better understanding of a still very obscure subject. I have not discussed the very controversial subject of burns toxins and antitoxins supposed to be present in convalescent sera. There is some evidence from various quarters that various antigenic substances can be produced at the site of thermal injury, these in turn could and apparently in some instances do lead to the appearance of corresponding antibodies.

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