THE PLACE OF IMMUNOTHERAPY IN THE MANAGEMENT OF EXTENSIVE BURNS

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Suggestions from earlier workers seemed to indicate that in burned tissue a specific antigen developed which stimulated the formation of an antibody a short while after receipt of the injury. If this hypothesis is correct, then plasma from a convalescent burn, if given to a recent injury, should reduce the effect of the trauma. However, positive evidence *in vitro* was required to prove the existence of a 'burn antigen' and 'burn antibody'. An investigation was therefore instituted in the Regional Blood Transfusion Centre, Edinburgh, using sera from recent and convalescent cases of burns treated in the Department of Plastic Surgery at the Royal Hospital for Sick Children, Edinburgh. This paper records these studies, discusses the results and reviews the literature on immunotherapy in the management of the extensive burn.

METHOD

Diffusion plates were prepared using 15 ml. of 1·5% agar in barbitone pH 8·6 (u=0·05). Anti-whole human serum was used to indicate a definite positive reaction. Serum samples were chosen from 5 patients in different stages of recovery from extensive burns and these were set to diffuse against a serum sample from a case of extensive burns only 20-hours old. The results are shown in Fig. 1.

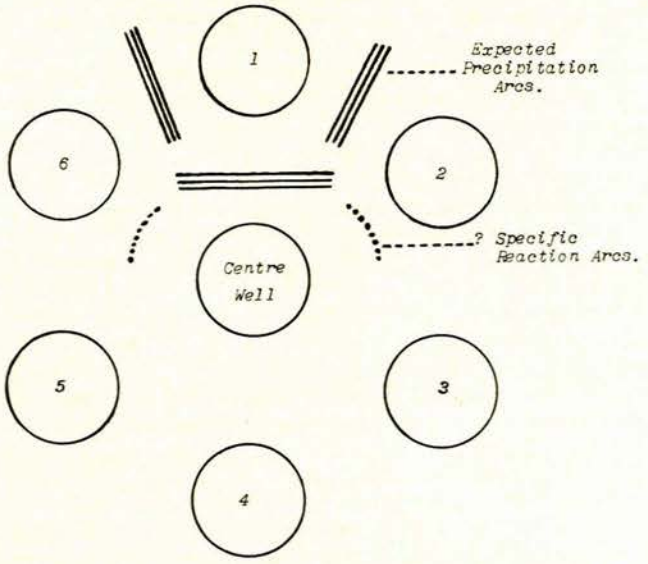

Fig. 1. Agar diffusion of burn sera. Note expected precipitation arcs between anti-whole human globulin and the 2 adjacent sera (Y.Y. and M.K.). Faint reaction arcs between serum from recent burn (Dryden) and the 2 adjacent convalescent sera (Y.Y. and M.K.).

Key:

Centre well	Dryden	20 hours post-burn.
Well (1)	Anti-whole human serum	
,, (2)	M.K.	24 days post-burn.
,, (3)	C.S.	61 days post-burn.
,, (4)	G.S.	30 days post-burn.
,, (5)	R.W.	44 days post-burn.
,, (6)	Y.Y.	47 days post-burn.

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Immunoelectrophoresis of the 6 sera involved in the diffusion plate was then carried out and any possible increases in proteins noted. Photographs of 3 of the sera tested are shown in Fig. 2. Further immunoelectrophoretic

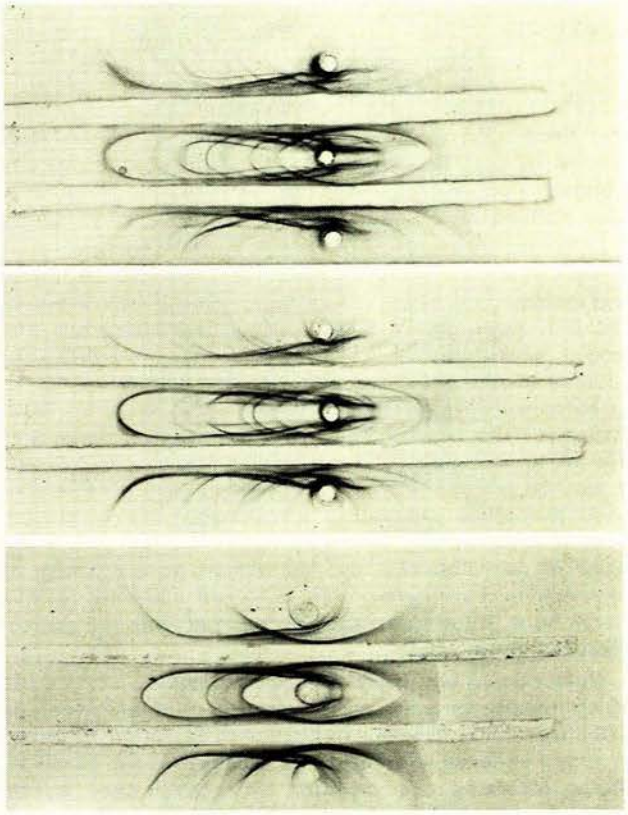

Fig. 2. Comparison of specific immunoelectrophoresis slides. Top: M.K. Centre: Dryden. Lower: Y.Y. *Analysis*: Top: increased B-lipoprotein, increased γ_1M globulin (19S). Centre: increased B-lipoprotein, increased haptoglobulin, slight increase γ_1M globulin and γ_2A globulin; possible $\gamma_1$globulin increase. Lower: approximately normal level B-lipoprotein and γ_1M globulin.

studies were carried out using a variety of serum samples but replacing the anti-whole human serum by serum from a recent burn. This was done in order to concentrate any antibody in the convalescent sera, thereby increasing the possibility of producing a positive reaction.

RESULTS

Agar Diffusion

Besides the expected precipitation arcs between the anti-whole human serum and the 2 adjacent convalescent burn sera, faint extra arcs between 2 of the convalescent sera (M.K. and Y.Y. in Fig. 1) and serum from a recent burn (Dryden, Fig. 1) were present.

Immunoelectrophoresis

The results from the 6 sera were as follows:

Patient	*Time after injury*	*B-lipoprotein*	*19 S γ_1M globulin*
Dryden	20 hours	?+	?+
M.K.	24 days	?+	?+
C.S.	61 days	+++	++
G.S.	30 days	++	++
R.W.	44 days	+	+
Y.Y.	47 days	+	—

As can be seen, the experiments were not really conclusive and no specific reactions were recorded. Studies on adsorption of antigen-antibody were carried out but with equally little success.

DISCUSSION

In 1876 Avdakoff[1] found that the blood of burned animals was toxic if injected into healthy animals of the same species. In 1952 Simonart[2] repeated these experiments and indicated that the enzymatic hydrolysis of the serum proteins resulted in a toxic substance similar in nature to the euglobulin fraction extracted from burn exudate.

With modern therapy few patients suffering from severe and extensive burns die in the initial phase of resuscitation. Death is more likely to occur later during the first and second weeks following receipt of the injury. Besides the obvious effects of infection, one of the factors considered to be responsible for this mortality is the so-called 'burn toxaemia'. The condition is supposed to follow the absorption of toxic products of autolysis of the necrotic tissue. It may be possible that some of these toxins possess antigenic properties stimulating specific antibody formation. Since it is most likely that maximum antibody titre would occur in convalescence, the transfusion of a quantity of convalescent burn serum into a patient suffering from a severe burn, would have the effect of reducing the general effects of the injury.

Work carried out in the Eastern European countries and which initially served to focus attention on immunotherapy in the treatment of burns, was reported in optimistic terms. In 1956 Feodorov and Skurkovich[3] described the beneficial effects following the injection of convalescent serum. Patients so treated became more active, their temperature and leucocytosis fell and wound healing was more rapid.

In 1964 Blocker *et al.*[4] described an investigation carried out in their laboratories wherein burn serum was administered to a number of dogs with standardized scalds. The convalescent serum had been obtained from dogs which had sustained 20% scalds within the previous 3 months. The results, assessed by changes in the pulse, temperature, blood pressure, cardiac output and the electroencephalogram, were of limited interest. They failed to show that convalescent burn serum was of any value or benefit. An interesting incidental finding was a fall in the cardiac output and blood pressure immediately after a severe burn despite correction of hypovolaemia.

Blocker considered this to be the result of a 'toxic myocarditis'; it was however unaffected by the administration of convalescent burn serum. It is of interest to recall that Fozzard[5] had earlier drawn attention to the value of digitalis in the management of the severe burn.

In a recent paper[6] Craig published the results of a clinical trial of frozen convalescent serum obtained from extensively burned patients 3 - 6 months after injury. Ten children under the age of 10 years, all suffering from severe and extensive burns, were transfused daily for a week commencing 48 hours after injury. Efficacy was assessed on the mortality rate, duration of survival, level of leucocyte count and the presence of a positive blood culture. Of the series not 1 case survived, death being due in each instance to intercurrent infection most frequently involving the respiratory tract; there was no difference in the duration of survival between the test and control series; no definite pattern existed in so far as the leucocyte levels were concerned; finally there was no difference in the incidence of positive blood cultures.

Craig concluded that there was a possibility that freezing destroyed any active principle in convalescent serum; if so, then the practical effects of administering convalescent serum were greatly limited because of the difficulty in obtaining fresh serum for each new case of thermal trauma. If freezing did not exert any ill-effect, then it would appear that there was no benefit or value in the use of convalescent serum.

In the appraisal of Craig's results and conclusions, the observations of Malm and Slawikowski,[7] based on work done at the Walter Reed Army Institute of Research, should be borne in mind. These workers felt that the effects of convalescent serum could not be measured in terms of differences in survival rate in the early post-burn period; should a 'burn antibody' exist, its effects would be related to morbid rather than lethal factors.

The argument as to whether a 'burn antibody' exists has been waged in the laboratory as well as in the ward. In 1962 Dobrkovsky *et al.*[8] reported a series of 30 cases in which by means of a latex agglutination technique, antibodies against burned skin were demonstrated on the 3rd - 8th post-burn day. Titres gradually fell until by the 6th month no antibodies were found in the circulating blood. Rosenthal *et al.*[9] claimed the presence of immune bodies in the plasma of burned patients by means of a precipitation technique. Artussen and Fjellstrom[10] showed that there was reduction in complement towards the end of the 1st week in the severe burn. Although they admit that there may be many reasons for this, they suggest that the reduction may be due to fixation following antigen-antibody reactions. On our own studies, no specific reactions were recorded to indicate the presence of a 'burn antibody' in the cases under investigation. The consistent increase of B-lipoprotein was not considered immunologically significant.

The National Research Council of America has issued a directive in which it states that no statistically acceptable evidence for the support of a burn toxin-antitoxin exists. The clinical evidence, at least that which is produced by workers in Western countries, seems to concur with this point of view. Bacteriologically, the findings are equivocal. It would appear that the view expressed by Virginia Blocker,[11] namely that the possible benefits from 'immunotransfusions' are related to antibodies against microorganisms rather than to true 'burn antigens', may be the answer to the problem. From the results of our own investigations, we find ourselves in agreement with this opinion.

CONCLUSIONS

The question of the existence of a 'burn toxin' with its specific antitoxin has been strongly debated over the last decade.

Although clinical evidence produced by workers in Eastern European countries originally seemed to indicate that the use of convalescent burn serum in the management of the recent extensive burn was associated with a reduction in the effect of the injury, further enquiries into the problem by other workers has not confirmed this. At present it seems that whereas non-specific antibodies to microorganisms may well occur in the circulation of the patient convalescing from an extensive burn, no true 'burn antibody' has been demonstrated. The routine use of convalescent burn serum is therefore of doubtful value.

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