exercise or excitement. The pain never wakens the patient during the night, although he may waken in the morning with it. This symptom, like all those mentioned in this report, is frequently associated with a change of environment. In many respects the photophobia runs parallel with the headache. It, too, may be unilateral, and be felt on the side on which, as the patient is aware, there is ocular inferiority. Dark glasses are often worn on days not much, if any, brighter than can be experienced on summer days in Britain. Their use appears to have a symbolic significance to the patient. As stated, muscae volitantes and epiphora are often associated with photophobia and headache. Like them, they are very variable in their incidence: days may pass without the patient experiencing them.

Before making the diagnosis of chronic anxiety state with ocular manifestations it is, of course, important to exclude organic disease. The media of the eyes, fundi, and tear ducts should be investigated.

It is interesting to note in connexion with the disturbance of autonomic control which is suspected to be the basis of this group of symptoms, that a number of cases presenting the syndrome of headache, epiphora, and photophobia later develop exophthalmos with a well-marked von Graefe sign. In them there is not necessarily thyroid enlargement or increase in pulse rate. As mentioned above, such cases may have a partial loss of convergence, with diplopia.

Treatment of Chronic Anxiety State with Ocular Manifestations

The treatment of chronic anxiety state with ocular manifestations is more satisfactory than that of ocular hysteria, and in many cases can be satisfactorily carried out by the ophthalmologist. The qualities required are patience, kindness, and directness. It is easy to advocate these qualities, though difficult to show them in the rush of the clinic. Nevertheless no good treatment of the chronic anxiety state can be carried out without them. There must be patience to listen to the man's story, to watch his mind during the examination, to evoke his past life and environment, and to interrogate his emotions so that the hidden anxiety state may be exposed. This must not be done in a gruff manner, otherwise the patient becomes defensive and more tongue-tied than ever. There must be directness to impress him that no disease of the eyes is present and to indicate the manner in which the symptoms arose. There are few patients who do not intelligently and emotionally respond to this treatment.

Summary and Conclusions

In this report mention has been made of (a) the two chief psychical conditions—hysteria and chronic anxiety state—which cause a variety of ocular symptoms; and (b) the differentiation of these functional symptoms from those produced by organic disease.

For clarity the psychosomatic processes have been described as well-defined entities. These processes are personality reactions, and although the individual may show a tendency to react in a certain way, personality is too complex for the reaction to be simple and uniform. In practice many a case does not fit into a clear-cut pattern. An obvious hysteric may develop symptoms described above as chronic anxiety state with ocular manifestations, while a case with hysterical symptoms in the eyes may have a well-developed chronic anxiety state. Moreover, the difficulty is not only as between one functional condition and another. Both an organic and a functional condition may be present in the same patient. Their relative significance in the production of the symptoms is of therapeutic importance. Only a very careful physical examination together with some considerations along the lines indicated above, and the experience of the examiner, can help disentangle the threads.

It may be of some help to think of organic and functional disturbances coexisting in one of three different ways: (1) The association in one patient may be fortuitous. (2) A functional disturbance may be superimposed upon an organic one, modifying or aggravating the symptoms. (3) The psychic disturbance leading to upset of ocular function may appear to be an integral part of the organic process. This is noticed in disseminated sclerosis. It is not unusual in this disease for the "functional" symptom to be the predominant one and to be present for a long period before the "organic" symptoms arise.

I would like to express my thanks to Brigadier C. W. Graham, Consultant Ophthalmologist, Brigadier G. W. B. James, Consultant Psychiatrist, M.E., Major J. M. M. Jacobs, and the staff of No. 2 Psychiatric Centre for their generous guidance and help. Many of the cases were diagnosed and treated in No. 2 Psychiatric Centre.

HUMAN FIBRIN AS A DRESSING FOR BURNS*

BY

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The copious and continued oozing of fluid from a superficial burn is a curious contrast to the behaviour of an abrasion, which soon becomes covered by a scab of dried and clotted exudate. It is clear that the normal mechanism of haemostasis is unable to control the exudation of plasma from the capillaries at the surface of a burnt area. It is a temptation to think that the delay in healing of such burns as compared with abrasions of equal magnitude may be the result of this continued oozing, since in the haemorrhagic states even minute wounds may refuse to heal for weeks unless leakage of blood is stopped by suitable treatment. It is certain that in severe cases the loss of fluid from the burnt area may be so great as seriously to aggravate haemoconcentration, and a practical method of controlling this loss would be of clinical importance.

Attempts were made, therefore, to control this exudation by means that are usually successful in controlling the exudation of blood in the haemorrhagic states. To begin with, various coagulants, such as Russell viper venom and thrombin, were applied to the surface of burns, but any hastening of coagulation that was produced appeared ineffective.

It was observed that blisters forming soon after a burn usually contained masses of loose trabeculated fibrin that had no controlling effect on the exudation of fluid. The "blister fluid" that was drawn off and examined contained a further small amount of fibrinogen and often underwent secondary clotting in the test-tube, suggesting that the clotting mechanism was not seriously deranged. Unfortunately it was not possible to make quantitative estimations of fibrinogen and prothrombin on the exudate before it had partially clotted. Experiments with blister fluid showed that it differed little from the patient's serum. Titration of the immediate antithrombin, the progressive antithrombin, and fibrinolysis gave results essentially the same as those obtained with the blood serum. From these observations it appeared that the continued exudation of fluid might be the result not of defective coagulation but of a capillary defect, so that the local condition might be analogous to the continued bleeding in the purpuras, in which coagulation is normal. No effect would therefore be expected from the mere addition of coagulants to the issuing fluid: as in the purpuras, the flow must be stopped by mechanical means.

It was therefore decided to attempt to seal the burnt surface with some relatively impervious dressing. Human fibrin was chosen as the physiological ideal, and it was hoped that its presence might reproduce the conditions in traumatic wounds and encourage healing. After unsuccessful attempts to produce a sufficiently tough and adherent membrane by covering the burn with concentrated fibrinogen solution, or dried fibrinogen subsequently clotted by a spray of thrombin, it was decided to preform the fibrin membranes and apply them when required.

Preparation of the Fibrin Membrane

The technique that finally evolved was as follows: Human plasma was allowed to clot in flat shallow dishes. The ordinary photographer's earthenware developing-dish about 12 in. by 10 in. was found satisfactory. Before adding the plasma the dish was levelled with a spirit level in order to ensure even thickness of the membrane. About 450 c.cm. of plasma was used for each membrane, and this was mixed with 100 c.cm. of 1.18% CaCl_2 and 0.5 c.cm. of 1 in 100,000 Russell viper venom, in a large measuring cylinder. The mixture was rapidly poured into the dish and any large bubbles burst with a hot wire. Firm coagulation usually took place in from a half to one minute. The clotted plasma was allowed to stand for 30 minutes and was then covered with about 500 c.cm. of tap-water. By gently rocking the dish the clot was detached from the sides so that it floated freely in the water. It was

* A report to the Burns Subcommittee of the M.R.C. War Wounds Committee.

then covered with a sheet of blotting-paper cut to fit the dish, and this in turn by a sheet of perforated zinc of the same size. By pressure on this sheet much of the serum in the clot could be squeezed through the blotting-paper and perforations. Water and serum were then poured away, and by careful inversion the clot was turned out, lying on the blotting-paper and zinc. These were now laid on a draining-board, and the upper surface of the clot covered by another sheet of blotting-paper and perforated zinc. Pressure on this expressed the remainder of the serum.

On removing the blotting-paper the clot was found to have been compressed into a thin sheet of yellowish fibrin. This was carefully washed in water until white, and then pressed between sheets of dry blotting-paper. The finished membrane is a tough, elastic, glistening white sheet when wet; when dry it becomes transparent and brittle.

Sterilization of the Membranes

The membranes, suspended in saline in small screw-capped bottles, were usually treated by heat. Though they resist boiling, the fibrin becomes thickened and waterlogged and loses much of its elasticity. Heating to 80° C. for one hour or 70° C. for two hours was found to be less deleterious and to kill non-sporing pathogens incorporated experimentally in the fibrin, and this treatment was used throughout the clinical trials.

In Dr. Colebrook's laboratory experiments on sterilization by antiseptics and bacteriostatics were carried out. Small experimental membranes were made from plasma to which cultures of *Staph. aureus*, *Bact. coli*, streptococci, and *Ps. pyocyaneus* had been added. These infected membranes were incubated for varying periods in different concentrations of C.T.A.B. (cetyltrimethylammonium bromide), 2:7-diaminoacridine, dettol, sodium sulphacetamide, sulphanilamide, etc. The pieces of fibrin were then removed from the solution, washed in sterile water, and planted out in broth. It was found that the C.T.A.B. completely dissolved the fibrin in 24 hours, and even after three hours the membrane was partly destroyed. The organisms were not killed by three hours' immersion in 1.5% C.T.A.B. 24 hours' immersion in 30% dettol sterilized the membrane, but also partly destroyed it. Sulphanilamide (2%) and sodium sulphacetamide (20%) did not damage the membrane, but organisms were still viable after 24 hours.

The 2:7-diaminoacridine stained the membrane a bright red, but did not impair its properties. 24 hours' immersion in this substance killed all the organisms named when the dye was in concentration of 1 in 1,000. When it was reduced to 1 in 10,000 the coliform organisms and staphylococci remained viable.

Preservation of the Membrane

All the membranes used in the clinical trials had been "pasteurized" by heat. One, in addition, had been preserved in 1 in 10,000 diaminoacridine. After two or three weeks' immersion in saline, even in the refrigerator, membranes begin to lose their toughness and finally to disintegrate. Various preservatives have been tried without effect. Freezing the membranes retards the deterioration to some extent. In the dry state they appear to keep indefinitely and to regain their elasticity when soaked in water. They are so brittle when dry, however, that it is almost impossible to handle them without breaking, and as a method of preservation it was found impracticable.

Application of the Membranes

Several methods of sticking the membranes to the burnt surface by means of freshly formed fibrin were used, all of which gave firm adhesion. At first the burnt area, after being cleaned, was sprayed with fresh human plasma to which enough calcium chloride had been added to produce clotting in three or four minutes. The membrane was then spread over the surface, smoothed down, and the edges trimmed with scissors. Subsequently plasma was applied to the burn as before, but coagulation was produced by a solution of thrombin, in which the membrane had been soaked before application. In one case the membrane was applied over a burnt surface that had been covered with powdered fibrinogen, the membrane having been moistened with thrombin. This latter modification was not so successful, as the powdered fibrinogen contained air, which formed bubbles as it went into solution.

Clinical Results

Eight cases of accidental burns and two experimental burns have been treated by the application of about 17 sq. ft. of preformed membrane made from human fibrin. Two cases were in the Radcliffe Infirmary, under the care of Dr. J. M. Barnes; the remainder were at the Royal Infirmary, Glasgow, under the care of Mr. A. M. Clark and Dr. L. Colebrook. A brief summary of these is given below.

Case 1.—Male aged 31, admitted July 26, 1941, three hours after petrol burns of hands and forearms and circumference of right leg. The burns were cleaned under general anaesthesia; the hands and arms were encased in plaster and the leg was covered by a fibrin membrane over a film of recalcified plasma. A small area of the leg that could not be covered with fibrin was tanned. Within three hours the membrane had become transparent and a few drops of fluid exuded through it. For the next three days the membrane remained intact and firmly adherent, but the small tanned area began to suppurate. Then the centre part of the membrane softened and was digested, and culture from this area showed infection with *Staph. albus*. The membrane was removed, the area which was then granulating was powdered with sulphanilamide and penicillin, and a new membrane applied. This dried into a transparent scab, which began to flake off from the edges as new epithelium appeared. Healing was complete in 17 days. The plasters were removed from the hands and arms a day later, and here also healing was complete except for a few small blisters.

Case 2.—Male aged 19, admitted May 4, 1941, 24 hours after sustaining severe burns, multiple fractures, and lacerations in an aeroplane crash. The burns were treated by various methods. About 10 weeks after admission fibrin membranes were applied to four suppurating areas on legs and body. One of these was allowed to dry in air, and remained intact for three weeks, though a small amount of pus formed under a fold that had become detached. When removed there was evidence of active healing beneath it, and a second membrane was applied; but there was considerable formation of pus, and it was removed 12 days later without much evidence of further healing. Two other membranes were applied to suppurating areas on the chest and shoulders, and were kept moist by an oiled-silk dressing. In both cases the fibrin was completely digested over the whole of the raw area within 24 hours of application, and each area then healed within a few days without further applications.

Case 3.—Male aged 14 months, admitted Oct. 7, 1942, one hour after extensive scalding of back and thigh with boiling water. The burnt area was cleaned under general anaesthesia, and the upper two-thirds covered by a fibrin membrane, over plasma and thrombin. Sulphanilamide cream was applied to the remainder of the burnt area. During the next two hours there was some exudation of fluid from the area not covered by the membrane, though the membrane itself was dry. Two days later there was some elevation of small areas by collections of fluid beneath the fibrin, and five days after application part of the centre had been digested. Healing appeared to be almost complete under the peripheral parts of the membrane that remained. Seven days after the burn the membrane had flaked off and healing was progressing, except in the centre of the area originally covered, where there was a brown slough. The area of the burn treated with sulphanilamide cream appeared to be healing equally well. The sloughs finally separated nearly a month after the burn, and it was decided to graft that area.

Case 4.—Male aged 5, admitted Oct. 12, 1942, two hours after scalding scapular areas and buttocks with hot water. After cleaning, membranes were applied to the two burnt areas on the left side, those on the right being treated with sulphanilamide cream. Two days later it was found that the membranes had stuck to the gauze coverings and were only adherent in places to the burnt areas. There had been some discharge from this side. Four days after application the membranes became detached completely, leaving a clean surface that looked very similar to that on the other side, treated with cream. Healing on both sides was complete within two weeks.

Case 5.—Male aged 27, seen as an out-patient on Oct. 12, 1942, six hours after petrol burn of dorsum and fingers of right hand. The burnt area was cleaned and covered with fibrin membrane cut to fit, and bandaged over gauze. The membrane dried into a hard scab, which remained *in situ* for 10 days, when it separated, showing complete healing beneath.

Case 6.—Male aged 2, admitted Oct. 14, 1942, two hours after scalding chest and left arm with hot tea. After cleaning, a small area on the arm was covered with membrane, the rest being dressed with sulphanilamide cream. Within an hour of application the membrane became dry and transparent. Unfortunately the child died suddenly 11 hours later.

Case 7.—Male aged 5, admitted Oct. 15, 1942, two hours after scalding left arm, back left side, and left leg with hot water. After plasma transfusion the area was cleaned, the arm being covered with a fibrin membrane, the remainder dressed with sulphanilamide

cream. The membrane remained intact for eight days, when it separated. The lower part of the arm had healed; all the rest of the original burnt areas were covered by brownish sloughs, which separated 11 days later, leaving granulating surfaces, which it was decided to graft.

Case 8.—Female aged 27, seen as an out-patient 24 hours after scalding leg with boiling water. After cleaning, a membrane was applied, with almost immediately relief of pain. The membrane dried up, but two days later a small area in the centre became digested. Healing proceeded rapidly under the intact parts of the membrane, and was complete in 12 days.

Experimental Burns

Burns were produced on the upper part of the extensor surface of the forearms by the application of the end of a copper cylinder, 1 in. in diameter, through which hot water was flowing. The apparatus was devised by Prof. R. A. Peters (Leach, Peters, and Rossiter, 1943). The results are set out in tabular form below:

Subject I (R. G. M.)

Time	Left Arm	Right Arm
0	56° C. applied for 45 seconds Blistering and detachment of cuticle over whole area. Covered by fibrin membrane and left exposed to air. Immediate relief of pain.	56° C. for 50 seconds Blistering and detachment of cuticle over whole area. Covered by fibrin membrane, then by oiled silk to keep moist. Pain relieved.
30 mins.	Membrane has dried into hard transparent film where attached to skin; soft and pliable over burnt area. No pain.	Membrane unfortunately torn off when boarding a moving tram. Area oedematous and inflamed. Dressed with castor oil and sulphanilamide.
3 hours	Membrane dry and firmly attached. No oedema. No other covering. No pain or discomfort.	Painful and tender. Discharging pus. Redness over area 3 in. in diameter. Oedema over area 4 in. in diameter.
24 hours	Membrane covered with dry gauze and strapping to prevent accidental detachment. Perfectly comfortable and painless.	Re-dressed, with relief of pain. Painful and swollen. Culture: <i>Staph. aureus</i> .
48 hours	Apparently healed under membrane, which is now quite dry.	Oedema of whole forearm. Dressed with penicillin.
4 days	Membrane flaking off, leaving new epithelium. Completely healed.	Better, but still swollen and painful. Re-dressed.
6 days	—	As before.
8 days	—	Better; beginning to dry up.
10 days	—	Scab formation.
12 days	—	Scab flaking off, leaving new epithelium.
3 weeks	—	Healed.
4 weeks	—	Obvious scar.
9 months	No scar.	

Subject II (L. C.)

Time	Left Arm	Right Arm
0	56° C. for 60 seconds Detachment of cuticle. Dressed with sulphanilamide cream under oiled paper. Relief of pain.	56° C. for 60 seconds Detachment of cuticle. Dressed with fibrin membrane. Relief of pain.
40 mins.	No pain or swelling. Re-dressed as before.	No pain or swelling. Some leakage of fluid beneath loose corner of membrane.
24 hours	No pain, no swelling. Re-dressed as before.	No pain or swelling.
48 hours	Some inflammation and oedema round burn, which is covered by a film of yellow exudate. Allowed to dry in air.	Membrane dry and firm. No inflammation or oedema.
4 days	Dry and comfortable.	Some oedema and discomfort. Infected with <i>Staph. aureus</i> and diphtheroids. Fibrin membrane digested. Dressed with penicillin.
6 days		Hard scab.
9 days	Healed.	Healed.
11 days	—	—
12 days	—	—

Conclusions

It is clear that the covering of burnt areas with an adhesive membrane of human fibrin is a comparatively easy procedure. From the results, however, it will be seen that any clinical advantage over orthodox treatment is so slight as to make the trouble involved in preparation and application hardly worth while. The membranes relieve pain rapidly and form comfortable dressings, but the same can be said equally of many other applications. They may, to a certain extent, reduce fluid loss during the first 24 hours, but it would probably be more economical to transfuse the patient with the plasma required to make the membrane. In the cases that became infected the membranes were rapidly lysed. In favourable cases

the membrane dried into a scab, and healing proceeded beneath this. Even so, however, healing did not appear to be much more rapid than was the case in other areas treated differently.*

The problem of the fluid loss from burnt areas still remains, and its causation is of obvious interest and importance. That it is due mainly to paralysis or disordered function of the capillaries seems probable. Attempts to restore this capillary function might be therapeutically profitable.

I wish to thank particularly Dr. L. Colebrook for his kindness and advice in Glasgow, Prof. J. W. S. Blacklock for providing laboratory accommodation, and Dr. J. M. Barnes for allowing me to apply this form of treatment to his cases in Oxford. I am also indebted to Prof. R. A. Peters for advice and interest. My gratitude is due to the Medical Research Council for financial assistance and to Glaxo Laboratories Ltd. for the gift of special apparatus that was used in the experiments on blood coagulation and the preparation of fibrin, thrombin, and fibrinogen.

REFERENCE

Leach, E. H., Peters, R. A., and Rossiter, R. J. (1943). *Quart. J. exp. Physiol.*, 32, 67.

OUTBREAK OF SANDFLY FEVER IN TWO GENERAL HOSPITALS IN THE MIDDLE EAST

BY

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From July 28 to the end of Oct., 1942, there was a severe and explosive outbreak of sandfly fever among the staffs of two general hospitals and among the patients admitted to one of them. These two hospitals came to a new station during the last week of July. They occupied newly made sites, side by side. Hospital A took over the site and patients of another hospital which had been working since early June, 1942. Hospital B did not receive patients until the beginning of September.

Within a few days of arrival members of the staff of both units began to get sandfly fever, other ranks being more affected than officers and sisters. Later, patients who had been admitted to Hospital A for other complaints contracted the disease. By the end of August the epidemic had become serious. It ceased abruptly at the end of October.

Incidence of Sandfly Fever among Unit Personnel

Several of the "other ranks" had two or more attacks, which explains why the total number of admissions exceeded the

* Since submitting this report I have learned through the Medical Research Council that Ingraham and Perring of Harvard Medical School are using fibrin membranes "plasticized" by glycerol to prevent them becoming brittle, and sometimes backed with cotton. These improved membranes have given good results as a dressing for burns, and particularly as a dural substitute in brain surgery. Fibrin has also been used as a haemostatic. I have used small pieces of fibrin membrane soaked in thrombin as a haemostatic dressing for haemophilic cases with very encouraging results.