ERYTHEMA MULTIFORME BULLOSA (STEVENS-JOHNSON SYNDROME)

Some observations on Pathogenesis and on Treatment with Cortisone and ACTH

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CASE No. 1.—Showing clinical state before treatment.

The symptom-complex known as Stevens-Johnson Syndrome has become commoner of late, possibly due to a greater awareness of it, or to the hypothesis, recently gaining ground, that it is a non-specific antigen-antibody reaction, which may occur at any age in certain individuals exposed to different sensitizing antigens—bacterial, viral or chemical.

Although first described in 1860 by Hebra, who classified it amongst the polymorphous erythemata, the numerous eponyms subsequently used in describing its various forms, have tended to confuse any understanding of its causation, and have focused undue attention on the morphology of the eruption.

The reports which follow deal with the condition

and its treatment as met with in a child, a young woman and a middle-aged man.

Case Reports

Case 1

P.O'C. a male child aged $4\frac{1}{2}$ years was admitted on 9.7.54. Eight weeks before he had complained of a sore throat so severe that diphtheria was considered. He was treated with sulphonamides (sulphadimidine), during which a rash lasting two weeks appeared. One week before admission 'the skin peeled from his hands and feet.' On 7.7.54 a morbilliform rash appeared on his face. He was given penicillin and 'Cremotresamide,' but the rash worsened and blisters appeared on 8.7.54.

His condition on admission is seen in the accompanying photograph. T.100.2, P.114, R.22. He was anxious and distressed. His eyes were closed with purulent exudate and oedema but the conjunctivae and corneae were clear. A blotchy maculopapular rash was present on the face, trunk and limbs. Recently ruptured blebs were present on the cheeks, scrotal region and glans penis. There were erosions on the lips and buccal mucosa.

Treatment. Local antiseptics—Aq. Gentian Violet 1 per cent., Argentiprotein 5 per cent. Chlortetracycline 5 G. Diphenhydramine 250 mg. 6-hourly. 11.7.54 Corticotrophin (ACTH) GEL 10mg. b.d. for 16 days.

Investigations. Skin and Eye Swabs—Staph. saprophyticus. Hb 96 per cent. White cells 6000. Polys 46 per cent. Lymphs 60 per cent. Monos 6 per cent.

Progress. No response to Chlortetracycline, but spontaneous regression of all blebs and erythema promptly occurred after ACTH. Within eight days all lesions had gone, leaving a brown blotchy pigmentation of the skin. There was no recurrence. He was discharged well on 10.8.54 after 32 days.

Complications due to ACTH—Mild hypertension 130/90. Moon facies: Pigmentation. Weight increase.

One month after discharge his B.P. was 110/60 and his face and weight were normal.

Case 2

R.B.—a female typist aged 25 years was admitted 4.10.54, complaining of an itchy rash on face and limbs for one week. She was a known epileptic and had been taking Sod. Hydantoinate gr. 1½ with phenobarbitone gr. ½ thrice daily for the past month. She had never taken these drugs before.

On admission—T.104.8, P.124, Resp.22. Large neck glands. Left upper and lower eyelids swollen and red. Nares red and excoriated: Buccal mucosa and lips showed numerous bleeding erosions and some unruptured blebs. Scattered confluent erythematous macular lesions on the trunk; similar but discrete lesions on the limbs. No skin blebs present. Nikolski's sign negative. B.P. 110/70.

Investigations. Hb. 92 per cent., White cells 7600, Polys 70 per cent., Lymphs 20 per cent., Monos 9 per cent., Eos 1 per cent. Skin Swab—No growth. Eye Swabs—A few Staph: pyogenes grown. X-rays skull and chest, E.C.G.—normal. E.E.G.—frequent theta activity with sharp waves and spikes in the posterior temporal region during sleep.

Treatment. Aq. Gentian Violet 1 per cent. locally. Corticotrophin GEL 25 units 12-hourly

for six days. 1 per cent. Cortisone Eye Ointment to eyelids. 2.5 per cent. Hydrocortisone ointment to lips.

Progress. Gradual regression of all skin and mucosal lesions with spontaneous reabsorption of bullous fluid. Some residual brownish pigmentation. Discharged well 5.11.54, after 32 days. Complications of ACTH—Only pigmentation.

Case 3

J.B.—a male clerk aged 53 years. Admitted 3.4.54 with the story that one week previously he had complained of malaise and tightness of the chest lasting three days. He was treated with Dover's powder, 'Benadryl' and Aspirin and returned to work. On the day of admission he was hoarse and was 'covered with a rash, said to be measles.' He had had a L. nephrectomy nine years previously for stone and hydronephrosis.

On admission—T.102.6, P.116, Resp.16, Ill, Pale. Conjunctivae red. Labial mucosa ulcerated at the angle of the mouth. Pharynx, buccal mucosa and tongue very red, no blebs seen, but discrete yellow ulcerated areas were present opposite the lower molar teeth.

Brilliant dusky red maculopapular rash maximal on upper chest and back, scanty on forehead, neck and limbs but absent on face. Operation scar L. flank. B.P. 130/70.

Investigations. White cells 13,600. Polys 80 per cent (many juvenile forms). Throat and nose swabs—Staph. Pyogenes isolated.

Treatment. Two Courses of Benzyl-penicillin intramuscularly (1) 500,000 units 6-hourly for 48 hours. (2) 2,000,000 units 6-hourly for 24 hours. Diphenhydramine 25 mg. thrice daily. Aq. Gentian Violet 1 per cent. locally. Soluble Corticotrophin 25 units intramuscularly 4-hourly until death occurred, i.e. for 24 hours.

Progress. Although the temperature settled in three days, toxæmia and rash increased in intensity. Two days after admission ulceration of the penile meatus occurred. On 10.4.54 a few bullae were present on neck and arms; he was cyanosed with a weak and thready pulse—B.P. 90/60. He died on 11.4.54 after eight days. Necropsy was done, the main positive findings being:—Purple macular rash of limbs and shoulders; ruptured bullae on neck and arms; superficial ulcers of lips and palate.

Lungs: Milky yellow pus in air-passages; confluent bronchopneumonia of R. lower lobe with some similar patchy areas in the R. upper and L. lower lobes.

Heart: Slight left ventricular hypertrophy; coronary arteries patent; moderate atheroma of aorta.

Liver: Congested.

Discussion

The cause of Stevens-Johnson Syndrome remains obscure, but the fact that it would seem to follow an infection (Neale, 1948 and others) or a drug, e.g. phenobarbitone (Moss *et al.*, 1942), or an immunization procedure, e.g. tetanus, smallpox (Schwartz *et al.*, 1946; Grant, 1953), points to the development of an abnormal and sometimes lethal antigen-antibody reaction. This is supported by the cases presented (Cases 1 and 3—infection. Case 2—drugs—hydantoin and phenobarbitone). None relapsed, but although unusual, subsequent attacks of lesser intensity may occur months or years after the initial illness (Sneddon, 1947). This is also in keeping with an abnormal antibody effect. If this be so, it is necessary to postulate a time-interval during which antibodies appear in the circulation. In recently reported cases in this country (Davies, 1953; Caldwell, 1953; Grant, 1953; Wallace, 1954), symptoms appeared in from 2 to 10 days after the initial illness occurred. In the three cases herewith described, symptoms commenced seven days before admission. It is well known that serum-sickness develops up to 12 days after the introduction of foreign protein into the body. This supports the suggestion that a critical time-lapse up to ten days or so occurs before symptoms are noticed.

Various workers have described the histopathological appearances present, and these lend weight to an 'allergic' hypothesis. Howard *et al.* (1948) have described slight acantholysis and hyperkeratosis of the epidermis and corium, in which focal dilatation of capillaries and venules was present. In the subcutis fibrous trabeculae with irregular fine scarring were evident—lymphocytes, neutrophils, eosinophils and lipid-containing macrophages lay between the trabeculae. Agostas *et al.* (1952) noted perivascular lymphocyte infiltration of the corium, while Goldfarb (1946) described non-specific inflammatory changes, and noted the presence of eosinophilia. No eosinophilia, however, occurred in the present series.

Edgar *et al.* (1938) inoculated vesicle fluid into a guinea pig which developed anaphylaxis, but whether this was due to the presence of an abnormal substance or to the presence of human protein itself is debatable. Culture of the vesicle fluid, blood and spinal fluid is normally sterile unless secondary infection occurs, as in Cases 1 and 2 in which staphylococci—the commonest contaminants—were grown from the bullae. These negative findings are strongly against the hypothesis that the condition is a communicable infection due to a virus or bacterial agent. No record of case-to-case transfer has to my knowledge been recorded and this together with the

evidence implicating a multiplicity of agents is also in keeping with a non-infective cause. The disease is normally self-limited, lasting up to two months, but this, however, does not of itself exclude infection as a cause.

There are no characteristic general or local microscopic or macroscopic findings. This is exemplified by Case No. 3, in which the cause of death was bronchopneumonia.

The brunt of visible stress is borne by the skin and mucosae of the eyes, mouth and genitalia. Histamine is present in large amounts in these organs, but whether release of this or a similar substance by the abnormal reaction is ultimately responsible for the concentration of signs in these areas is debatable, especially as antihistaminic drugs seem to have no effect.

The illness bears some resemblance to more chronic bullous eruptions especially pemphigus vulgaris, but, unlike this condition there is no constant acantholysis, Nikolski's pinch test being consistently negative as in the present cases. Chlortetracycline has some effect in pemphigus vulgaris (Bettley, 1951), but no consistent effect in Stevens-Johnson Syndrome has been recorded. This applies, too, to other antibiotics and sulphonamides, which may even precipitate the condition (Agostas *et al.*, 1952). Chlortetracycline was without effect in Case No. 1 and penicillin in Case No. 3.

The fact remains, however, that both ACTH and Cortisone, when used early enough quickly cause regression of the lesions and reabsorption of the bullous fluid. In Case No. 3, ACTH was probably given too late in the illness after irreversible changes occurred. Cortisone has been used topically (Fishman, 1951), but, although of use in controlling obstinate isolated local lesions of the eyes, lips or genitals, systemic administration would appear to be more rational. The dose of ACTH or Cortisone must remain a matter of individual judgment and experience. A course lasting seven days, however, should suffice for the average case. Whether ACTH or Cortisone is the better also remains to be seen. The latter would seem to commend itself, because it can be given orally. I have had, as yet, no personal experience of its use. A short course should not cause any lasting toxic effects, thus, a mild Cushing-like syndrome developed in Case No. 1, but subsided quickly on discontinuing the drug. Brownish pigmentation of the lesions worried the female patient (No. 2), but it eventually faded. This latter effect may be avoided by using Cortisone, although it is possible that further purification of ACTH may eliminate it. On the other hand, routine employment of antibiotics would seem to be unnecessary as a prophylactic measure.

although they are of value in the presence of secondary infection.

Some speculation on the mechanism of absorption of the vesicle fluid may be profitable at this point. It is generally held that both ACTH and Cortisone cause retention of sodium and consequently body water. Fragility of the dermal intercellular bridges (acantholysis) has been demonstrated by Howard, as mentioned in the foregoing. This could lead to a leak of extracellular water into the superficial layers of the skin, thus causing a bleb. ACTH and Cortisone by retaining body sodium and raising body fluid tonicity may attract the bleb water back into the general tissue fluid again. Unfortunately, I could not arrange to test the tonicity or chemical content of the vesicle or body fluids, but I have no doubt that their examination would well repay study.

An alternative and probably more attractive hypothesis involves the nature of connective tissue itself rather than a mechanical water leak, although doubtless it could influence the latter. Robb-Smith (1954) puts the matter in perspective by rightly stating that 'the idea that the extracellular fluid is a stagnant pool of salt water whose character is determined by osmosis must be abandoned.'

He defines connective tissue as 'tissue fluid in a matrix of mucopolysaccharides and scleroproteins in varying degrees of polymerization but largely disorientated, on which are lying orientated films of varying thickness of collagen and elastica.' He stresses its dynamic nature and metabolic function. It is the latter aspect which might well be disturbed in Stevens-Johnson Syndrome. The extensibility of connective tissue depends on the water content, but whether the ultimate disturbance is related to this or to a more general metabolic upset, e.g. depolymerization, is conjectural. The effect of cortisone on connective tissue is antianabolic, but where fibroblasts are present, collagen and ground substances are laid down and connective tissue matures. Robb-Smith also speculates as to whether these hormones *directly* modify water and electrolyte changes, or do so *indirectly* by influencing changes in bound-water resultant upon depolymerization of the mucopolysaccharides and scleroproteins.

In the normal immune response, antibodies will be present in the ground substance to react with parenterally introduced antigens. In serum sickness a reaction occurs between fused tissue antibody and circulating antigen, which leaks slowly into the circulation, thus avoiding the shock of anaphylaxis, which results from a sudden flood of circulating antigen. The mechanism of drug allergy is probably the same, except a conjugate of the drug with the body protein, i.e. a Hapten

is necessary to form the allergen. The antibody, however, is probably confined to the tissue cells (Gladstone, 1953). Urbach (1946) believes this can be shown by injection of blister fluid from a case of atopic sensitivity into normal skin, in which a delayed indurated reaction occurs after 24 hours. Unfortunately, similar tests were not performed in any of the cases described, but Edgar's guinea pig experiments may be recalled here in this respect. Whether these results indicate the presence of reagins in the antibodies resulting from passive antigen transfer is debatable. In drug atopy they are usually absent in any case (Gladstone, 1953), so that it would be difficult to implicate them as the cause of Stevens-Johnson Syndrome. Anti-histamine drugs are of value in atopy but seem without effect in Stevens-Johnson Syndrome. This, as mentioned before, is indirect evidence that histamine release itself is probably not the cause of the syndrome.

As recovery or death is the rule, no evidence of permanent lesions has been produced, such as focal arterial necrosis or cellular infiltration.

The blisters usually heal without scarring, but as the lesion only involves the horny layer of the epithelium, this is understandable. The deeper cell layers rapidly proliferate by mitosis and amoeboid movement and thus cover any gaps (Florey, 1953).

The value of Cortisone and ACTH which *delay* healing (due to suppression of the inflammatory response to wounding or to lack of Vitamin C), is therefore to some extent paradoxical but this effect may be counterbalanced by the fact that they also suppress allergic phenomena. This may well be the mode of action in this syndrome.

The effects of hypersensitivity on smooth muscle and capillary permeability cause the ground substance of connective tissue to become oedematous and probably depolymerizes the mucopolysaccharides (Robb-Smith, 1953). Cortisone is a glucocorticoid, i.e. a hormone which effects carbohydrate metabolism. Whether it acts by antagonizing the depolymerization of mucopolysaccharides remains to be proved.

Summary

Three cases of Stevens-Johnson Syndrome treated with Corticotrophin are described.

The pathogenesis of the condition is discussed and the evidence in favour of an abnormal antigen-antibody reaction as the cause is reviewed.

The mechanism of action of ACTH and Cortisone is also dealt with. It is concluded that Cortisone may act by antagonizing the depolymerization of the mucopolysaccharides in connective tissue resulting from the abnormal antigen-antibody reaction.

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Addendum

Campbell (1955) has described three further Australian cases of the syndrome, two of which were treated with Cortisone and ACTH. There was no response to ACTH but some response to Cortisone. The author is sceptical about the value of these agents, especially ACTH, in the treatment of the Syndrome. Personally, I feel that ACTH, i.e. pituitary stimulation, is not likely to be of value in extremely ill cases in whom depression of the target-organ (adrenals) may be so severe (as in my own fatal case) as to be unresponsive to stimulation. It is well known, too, that potency of batches of ACTH vary and the author may have been unfortunate in this regard.

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