THE HERPES SIMPLEX VIRUS IN INFANTILE ECZEMA

BY

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Infantile eczema is perhaps one of the most distressing afflictions of early life, frequently more so to the parents than to the victim. Treatment is always a problem; at home improvement is often slow, and in hospital other conditions, occasionally serious, are readily contracted. The damaged skin is frequently infected by bacterial "opportunists," and less often, though with apparently increasing frequency, by viruses, which may produce an acute vesicular eruption not unlike smallpox, with a high mortality rate. This complication of atopic eczema was first recorded by Kaposi in 1887, and there is little to add to his vivid description:

". . . an acute outbreak of numerous vesicles, partly scattered, partly arranged in groups. The vesicles are as large as a lentil, filled with clear serum, and the majority are umbilicated. They look like varicella lesions, but undoubtedly do not belong to this class. The integument which has been attacked in this manner now appears still more swollen, even tense. The little patients have a high fever and are very restless. The vesicles develop very acutely (sometimes overnight), in large numbers, and often continue to appear, in successive crops, for three or four days, or even a week. Those which appear first undergo desiccation, rupture, and expose the corium, or they become encrusted and fall off. The largest number of these varicella-like vesicles are found upon the already eczematous skin, but smaller groups appear upon the previously intact skin of the neighbourhood, upon the forehead, ears, neck, and even the shoulders and arms."

Kaposi originally suggested the title "eczema herpetiforme," but he suspected a fungus as the cause. The syndrome was first identified with the virus diseases by Juliusberg (1898), who, although confusing the issue himself, drew attention to the close resemblance of the individual lesions to vaccination pustules. Although the precise aetiology was subsequently disputed, by common consent the term "Kaposi's varicelliform eruption" became firmly established. The numerous reports during recent years have clearly demonstrated that this condition is a distinct entity, is commonly produced by the virus of either herpes simplex or vaccinia, and that, although rare, it may well be seen by many during their practising career (Whittle *et al.*, 1950). When due to vaccinia there is usually a history of recent vaccination or contact with recently vaccinated persons. In the absence of such contact it is likely to be due to herpes simplex, when a history of herpetic infection in a close contact is often obtained.

Several examples of both types have been seen recently. The object of this paper is to describe three typical cases and to review the published literature on the subject.

Case 1

A female infant aged 6 months, who had been immunized against diphtheria but not vaccinated, had suffered from infantile eczema in moderate form affecting both legs and face since the age of 3 months. Three days before admission she became listless and developed "blisters" behind both knees. She was admitted to the ward on April 13, 1953. When seen on April 15 she showed groups of umbilicated vesicles and pustules superimposed on the eczematous skin of the nape of the neck and both legs, some areas being extensively traumatized. There was considerable inguinal lymphadenopathy. Her temperature was 101.4° F. (38.6° C.), pulse 146, and respirations 36. No abnormality was detected in any system. She was transferred to the fever hospital on April 15. The child's father and grandmother had recently suffered from colds associated with "cold spots." In fact, the father's labial herpetic infection was still present.

Treatment consisted of aureomycin lotion locally, soluble penicillin, and, later, "distaquaine" systemically (Fig. 1). The child was acutely ill during the pyrexial phase. Crops of fresh umbilicated vesicles appeared daily, even on the gums. Recovery ensued without pitting or scarring. The basic eczema remains unchanged.

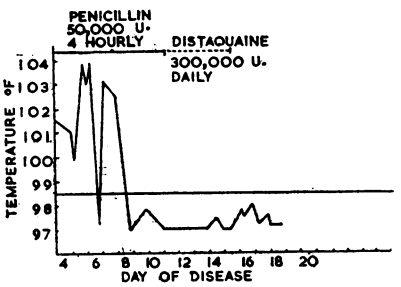

FIG. 1.—Chart of Case 1.

Investigations.—Blood: Hb, 85%; white cells, 8,000 per c.mm. (polymorphs 76%, lymphocytes 20%, monocytes 4%; no eosinophils or basophils). Films showed anisocytosis of red cells. Swab from vesicle: films showed Gram-positive cocci; culture showed *Staph. aureus.* Egg culture: positive for herpes simplex. Serum for herpes-neutralization tests: increase in herpes-neutralizing antibody titre between first and second specimens.

Case 2

A female infant aged 11 months, who had not been immunized or vaccinated, had suffered since the age of 3 months from moderately severe infantile eczema affecting the face and neck, for which she was in hospital when Case 1 was admitted (April 13, 1953). In the course of a routine ward round on April 20 comment was passed on this child's good luck in having escaped Kaposi's varicelliform eruption. Careful examination revealed nothing apart from her basic eczema. During the same evening she became listless and developed a temperature of 104° F. (40° C.), pulse 140, and respirations 40. One hour later crops of small clear vesicles were seen on the left shoulder and chest. The next day typical umbilicated vesicles and pustules were present. At first there was no lymphadenopathy, though this later became marked in the left axilla. The child was transferred to the fever hospital on April 21.

Treatment consisted of aureomycin lotion locally and penicillin and, later, aureomycin systemically (Fig. 2). The child was gravely ill during the pyrexial phase, fresh umbilicated vesicles appearing daily. Recovery ensued, but the basic eczema was unchanged. There are no pitted scars.

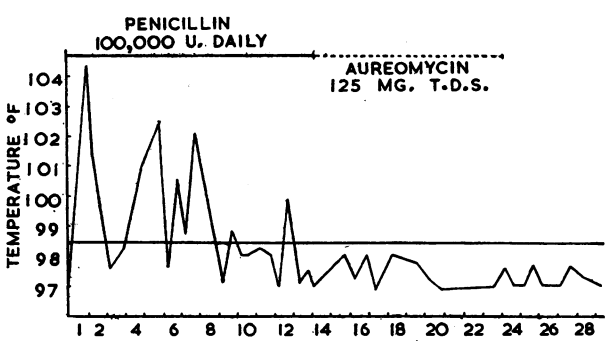

FIG. 2.—Chart of Case 2.

Investigations.—Blood : Hb, 80% ; white cells, 20,000 per c.mm. (polymorphs 62%, lymphocytes 25%, monocytes 13% ; no eosinophils or basophils). Films showed anisocytosis and microcytosis of red cells. Swab from vesicles : films showed Gram-positive cocci ; culture showed *Staph. albus.* Urine : N.A.D. Portable *x*-ray film of chest showed no lesion. Egg culture: positive for herpes simplex. Complement-fixation test negative for vaccinia-variola group. Serum for herpes-neutralization tests : increase in herpes-neutralizing-antibody titre between first and second specimens.

Case 3

A male infant aged 8 months, who had not been immunized or vaccinated, had suffered from xeroderma since birth and had developed scattered patches of eczema, for which he had received treatment at hospital. Both parents were vaccinated on May 14, 1953, but this was not attempted on the child because of the skin condition. Four days before admission—that is, on May 27—the child suddenly became listless, developed a high temperature, and later had "vaccination blisters" on the left arm. When admitted to the fever hospital on May 31 the left arm showed groups of umbilicated vesicles and pustules, with marked inflammatory reaction, and occasional vesicles on the right arm and legs. There was moderate axillary lymphadenopathy. His temperature was 101° F. (38.3° C.), pulse 138, and respirations 34. No abnormality was detected in any system. Treatment consisted of systemic penicillin and local aureomycin cream. Recovery was rapid and uneventful. The basic xeroderma was unaltered. There is some residual scarring.

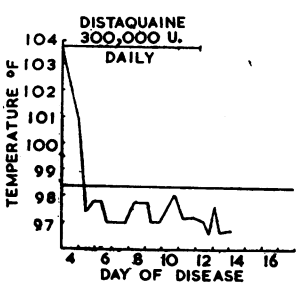

FIG. 3.—Chart of Case 3.

Investigations.—Blood: white cells, 13,600 per c.mm. (polymorphs 61%, lymphocytes 28%, monocytes 4%, eosinophils 7% ; no basophils). Swab from vesicles : haemolytic streptococci present. Egg culture : positive for vaccinia ; complement-fixation test positive for vaccinia-variola group. Serum for vaccinia-neutralization tests : increase in vaccinia-neutralizing-antibody titre between first and second specimens.

Diagnosis

The clinical diagnosis of virus eruptions in their typical form usually presents little difficulty. Confusion may arise because of pre-existing skin disease, particularly atopic eczema. Atypical forms of virus disease create further difficulties in diagnosis, especially during an outbreak of smallpox. In susceptible persons varicella, variola, and vaccinia, as well as herpes simplex and herpes zoster, should be considered, and, if excluded, some other virus sought.

The clinical diagnosis of eczema herpeticum in infants depends upon the sudden appearance of profound toxaemia, high temperature, and a pock-like eruption on eczematous skin. A history of recent herpetic infection in close contacts is often obtained. Cases are undoubtedly unrecognized or misdiagnosed, and the condition is probably commoner than reports indicate. In eczema vaccinatum the nature of the eruption and a history of recent vaccination or contact should suggest the diagnosis. The possibility of confusion with chickenpox is slight, but the resemblance to smallpox may be striking, especially if the face is affected. If possible, laboratory confirmation should be obtained.

The laboratory diagnosis of virus eruptions, although not easy, depends upon identification of the virus concerned after culture on the chorioallantoic membrane of fertile hens' eggs, or demonstration of its presence by complement-fixation tests. For both tests papule scrapings or vesicle fluid and crusts are required. Alternatively, the patient's serum may be used against known virus antigen. The complement-fixation tests are rapid ; egg culture is precise, but requires more time. Microscopical examination of smears of vesicle scrapings for elementary and inclusion bodies is rapid and, if positive, of considerable value. Biopsy and the demonstration of virus-neutralizing antibodies in the serum are of little value except in retrospect (Anderson, 1952).

For the laboratory, six to twelve "fresh" vesicle tops or scabs should be placed in a small sterile bottle. Vesicle fluid should be obtained in two or three capillary tubes (similar to those for vaccination lymph), which are sealed by flaming the ends, and then placed in a dry bottle. Smears may be made by scraping the bases of four to six lesions. The greater the quantity of material collected the better the interpretation of the results (MacCallum, 1952). If possible, two samples of clotted blood should be obtained —one during the first few days of illness and the other during the second to third week—in order to show a rise in serum antibody titre.

Treatment

There is as yet no effective form of antiviral treatment. Gamma globulin or transfusion of immune serum may be tried. Moccasin venom is mentioned by Barker and Hallinger (1947), but no other reports have been seen. Extensive cases should be watched for signs of fluid depletion, and corrected if necessary.

Despite varying reports, the recent antibiotics are probably equally effective, although differing from one case to another, in controlling secondary infection. The cases recorded here were given penicillin because the earlier cases had failed to respond to aureomycin. Sulphonamides should not be used, because there may be an actual or a relative leucopenia (Lane and Herold, 1944 ; Miller *et al.*, 1950). The value of A.C.T.H. and cortisone is still undecided, although one of the earlier cases developed eczema herpeticum whilst on small doses of A.C.T.H.

Locally, potassium permanganate soaks (1 : 100,000) are viricidal against vaccinia and variola (Gordon, 1941), and may be tried against herpes simplex. The viricidal action is inhibited by glycerin. Antibiotic creams or lotions should be used ; all of the present series appeared to benefit from local aureomycin.

The basic eczema, although temporarily improved, usually remains unaltered.

Prognosis

The prognosis of eczema herpeticum depends upon virus virulence, susceptibility of host, nature and extent of previous skin trauma, and secondary infection with its ensuing complications. All grades of severity occur, from mild abortive to extensive fatal cases (Lynch and Steves, 1947). Death may occur during the primary toxaemia, or later because of extensive secondary infection. Most of the deaths reported in eczema vaccinatum have been due to encephalitis or general sepsis (Perry and Martineau, 1949).

The mortality rate is variable. Blattner *et al.* (1945) state that the disease is self-limiting and in general the prognosis is good. O'Leary (1944) thinks that its seriousness should not be minimized, as the literature indicates that probably one out of every three children with eczema herpeticum dies, whereas in adults it is not so serious ; Sims and French (1948) report six deaths out of nine cases. None of the present series died, but at various times three (of six) cases were dangerously ill.

Communicability

All the pock viruses, including herpes simplex, are highly infectious, especially in the presence of eczema or other skin damage, when the reaction to primary infection may be unusually severe. The occasional epidemic outbreaks of eczema herpeticum are possibly due to an increase in virus virulence (Unger, 1947). In the presence of virus-neutralizing antibodies, recurrent lesions of herpes simplex may be due to local lowering of resistance (Varley and Kletz, 1949). The development of sore throats, vesico-pustules, and herpetic lesions in the attendant staff has been reported

(McLachlan and Gillespie, 1936; Barton and Brunsting, 1944). In the present series three nurses developed vesicopustules, which remained limited in extent on the hands and fingers and responded rapidly to local aureomycin. Virus studies were not made.

It is suggested that eczema herpeticum should be classed as a notifiable disease to ensure future epidemiological investigation.

Vaccination

As routine for public protection, vaccination is preferably performed by the multiple pressure method on the upper arm during the first six months of life. Despite cosmetic considerations the leg should be avoided, for it is almost impossible to keep an infant dry in this region, and the consequent skin damage predisposes to dangerous reactions.

There are certain contraindications to vaccination: it should not be attempted, on adult or child, in the presence of eczematous or otherwise damaged skin. The desirability of vaccinating the parents of children thus afflicted should be considered, and if attempted the vaccination site should be carefully occluded (Jeffs, 1952). Women should not be vaccinated during the first three months of pregnancy because of the significant increase in foetal mortality. There is virtually no risk during the later months of pregnancy (MacArthur, 1952).

Prevention

In view of their high infectivity to susceptible persons, cases of extensive eczema herpeticum and eczema vaccinatum should be isolated. Sufferers from atopic eczema should be warned of the danger of exposure, and safeguarded, if possible, from persons with active herpetic or vaccinial lesions, including, if infected, members of the medical and nursing staffs. Somerville *et al.* (1951) suggest that recently vaccinated persons should not be admitted to hospital, especially to a skin ward, without adequate precautions being taken. They suggest that during times of widespread vaccination it might be wise to discharge persons, especially children, suffering from allergic eczematous conditions. Normally, maternal antibodies in human milk protect infants up to the age of about 12 months: it may be that lack of this protection allows "ward" epidemics to occur. Mothers of infants in hospital should therefore be encouraged to continue breast-feeding.

Discussion

The cases described constitute a little-known clinical syndrome of which the main features are a sudden general disturbance and a pock-like eruption occurring on previously damaged skin. Hitherto the inclusive term "Kaposi's varicelliform eruption" has been used without qualification regarding the causative virus. Since there is little resemblance to chickenpox, it has been suggested that the term "Kaposi's varicelliform eruption" should be discarded in favour of "systemic herpes simplex" (Barker and Hallinger, 1947), "disseminated herpes simplex" (Sulzberger and Baer, 1948), or "eczema herpeticum" (Lynch, 1945) when due to the herpes simplex virus. Anderson (1949) has suggested the inclusive term "virus pyodermia."

The term "vaccinia" is used to denote the course of the eruption at the site of inoculation with the virus of vaccinia and the concurrent reaction of the body. Normally, the vesicular eruption is limited to that site, but rarely it may appear extensively over the body, for which the term "generalized vaccinia" has long been used (Jubb, 1943). About two-thirds of these cases have suffered from pre-existing skin disease, when the special title "eczema vaccinatum" is applied. There is no evidence to suggest that the remainder are due to "a latent unhealthy state of the skin" (Jubb, 1943).

Although not entirely satisfactory, but in order to obtain some degree of uniformity and to denote the association between damaged skin and inoculation with the virus of herpes simplex and vaccinia respectively, the terms "eczema herpeticum" and "eczema vaccinatum" are suggested.

The incidence of eczema herpeticum and eczema vaccinatum is higher among children, but adults are occasionally affected. In a review of the literature, Ruchman *et al.* (1947) state that of 96 reported cases 75 occurred in children, of whom 24 were under 1 year of age. The mortality rate was 23% in children and 9% in adults. Cases are normally sporadic, although epidemics occur in dermatological wards (McLachlan and Gillespie, 1936; Esser, 1941), and have been reported in paediatric and burns units (Nimpfer, 1936; Sims and French, 1948), indicating high infectivity to susceptible persons. Eczema herpeticum may be suspected in the absence of vaccination or known contacts.

A rise in the incidence of generalized vaccinia and eczema vaccinatum occurs when large numbers of people are vaccinated—for instance, following an outbreak of smallpox. Estimates have placed the incidence of generalized vaccinia at one in 20,000 to one in 96,000, and the mortality rate at 12% to 30% (Ross, 1940; Jubb, 1943).

During the course of approximately 50,000 recent vaccinations in the Bradford area at least five known cases of eczema vaccinatum have occurred, one being fatal (McDonagh, personal communication). Three were seen personally, one of which is described.

Since November, 1952, one case of eczema vaccinatum and six cases of eczema herpeticum, including the two reported, have occurred. There were no fatalities, but all the cases of eczema herpeticum were gravely ill, three of them, at one point, being considered moribund.

The lesions of eczema herpeticum were greater in number, more uniform in size, and of more widespread distribution than those of eczema vaccinatum, which showed close grouping of larger, firm, almost indurated vesicles of varying sizes with marked local inflammatory reaction. Crusts from herpetic vesicles were easily removable whole, whereas the vaccinial crusts were adherent, and when removed left frank bleeding surfaces. Lymphadenopathy was more pronounced in eczema herpeticum than eczema vaccinatum. In both types the eruption was maximal on eczematous areas, but occasional scattered lesions on apparently normal skin were seen. All the herpetic cases developed "chests" which gave rise to some concern. No corneal lesions occurred. Secondary infection was milder in eczema herpeticum, although it became severe in the later stages of the four earlier cases. It should be possible in the majority of cases to distinguish clinically between the herpetic and the vaccinial types (Lane and Herold, 1944; Lynch, 1945; Lynch and Steves, 1947), although other viruses may occasionally be causative (Anderson, 1949; Leverton and Whitlock, 1949; Brain *et al.*, 1950; Miller *et al.*, 1950; Whittle *et al.*, 1950; Leider, 1951).

The damaged skin is an ideal site for chance inoculation, not only because it presents a large raw surface but because the virus is thus afforded a wider choice of cells suitable for its continued existence. There is probably no immediate tissue response, as occurs with the pyogenic bacteria. This is possibly because the virus, depending upon an intracellular environment for growth and multiplication, allows cell metabolism to proceed normally until ultimate interference with enzyme mechanisms causes complete cellular disintegration, thus liberating the viruses into the tissue fluids. Subsequent haematogenous dissemination occurs, with localization of the viruses at sites of previous injury. This may account for the apparent lack of virus-neutralizing antibodies initially, with a rise in titre during convalescence (Ruchman *et al.*, 1947). This is illustrated by Case 2, in which there was a presumed maximum possible "incubation" period of seven days, during which the child was apparently quite well. When the first toxic sign appeared no eruption was visible, but almost within the hour herpetiform vesicles were uniformly distributed throughout the eczematous areas. All the present cases show a rise in virus-neutralizing-antibody titre, suggesting primary infections.

The association between previous injury and localization of lesions is well known—occurring, for example, in warts, lichen planus, and psoriasis, along the line of a scratch (Koebner's phenomenon).

Eczema herpeticum—and in parallel eczema vaccinatum and the vaccinia virus—represents one of the primary manifestations of herpes simplex infection (Kipping and Downie, 1948; Blank, 1949; Brain *et al.*, 1950) occurring in persons subject to a cutaneous allergic diathesis. It may well be regarded as a specific infectious disease with a short incubation period (Burnet and Williams, 1939). This infection normally occurs during childhood, and is not usually accompanied by severe reactions, though these sometimes occur (Kipping and Downie, 1948). The severity of these reactions may be due to anaphylaxis (Barker and Hallinger, 1947), although virus virulence, susceptibility of host, secondary infection, and the nature and extent of the preceding eruption are probably contributory factors (Lynch, 1945). There is probably synergic action between virus and bacteria (Lack, 1948), and the prognosis may ultimately depend upon this (Brain *et al.*, 1950). In the two cases of eczema herpeticum reported, secondary infection was comparatively mild, possibly because of early diagnosis and administration of antibiotics.

Lane and Herold (1944) suggest that eczema herpeticum occurs predominantly in persons who suffer from a definite and particular disease—for instance, atopic eczema. By contrast, eczema vaccinatum may be superimposed on many different primary diseases, inoculation occurring at a point of lowered resistance or altered epidermis. This is illustrated by Case 3, in which, despite the presence of xeroderma, there was no immediate history of preceding epidermal breach at the site of the eruption.

Although infantile eczema is a common disease, and the virus of herpes simplex widely distributed, eczema herpeticum remains a relatively rare condition. After primary infection the virus is thought to become latent and exist symbiotically with its host, being stimulated to fresh activity by other exciting agents—for example, trauma, infections, or even vaccination. Although the primary attack of herpes simplex often passes without notice, other manifestations occur, since more organs than the skin are affected (Wenner, 1944; Evans *et al.*, 1945; *Lancet*, 1952). These are many and varied, including all grades of severity from keratoconjunctivitis and mild stomatitis to fatal hepatic disease and encephalitis (Dodd *et al.*, 1938; Quilligan and Wilson, 1951; Florman and Mindlin, 1952). Many cases are probably unrecognized or misdiagnosed. It is feasible that, because the virus of herpes simplex prefers ectodermal tissue, infection may occur with equal frequency in the skin and central nervous system, thus accounting for several of the otherwise unexplained "temperatures" and mild toxic reactions which so commonly occur in children. Perhaps the well-known patch of "recurrent herpes simplex" which so consistently occupies its chosen site in the skin has its counterpart within the central nervous system.

Boake *et al.* (1951), reporting an adult case of recurrent eczema herpeticum, point out that, once infected, people are liable to recurrent attacks of herpes simplex, which vary in severity, frequency, and the stimulus required to produce them. Sulzberger (1945) suggested that some of the vesicular diseases of which little is at present known may be due to the virus of herpes simplex. Other forms of infection include herpetic paronychia, bullous herpes simplex of the fingers, and follicular and sycosiform herpes simplex of the beard area.

Miller *et al.* (1950) report a patient who contracted eczema herpeticum during the second to third month of pregnancy, and was subsequently delivered of an apparently normal infant. They discuss the possible role of the herpes simplex virus in the aetiology of congenital abnormalities. It is established that German measles contracted during the first three months of pregnancy is associated with a high incidence of foetal abnormalities (Gregg, 1941; Swan *et al.*, 1946). Wesselhoeft (1947) cites mumps, herpes zoster, scarlet fever, varicella, influenza, hepatitis, and poliomyelitis as causative factors in congenital abnormalities. The actual way they produce this effect is uncertain. It is significant that the diseases are mostly viral, and that the viruses of smallpox, chickenpox, and vaccinia may pass the placental barrier, causing death or giving rise to active foetal disease *in utero* (MacArthur, 1952). The virus of measles probably affects the foetal tissue directly, and it is reasonable to expect other viruses, including herpes simplex, to act similarly. This view is supported by France and Wilmers (1953), who report premature twin boys dying a few days after birth showing pathological features of herpetic hepatitis, and in one case encephalitis. Since no obvious portal of entry was found, they consider that infection was probably transplacental.

It is apparent that the manifestations of infection with the virus of herpes simplex vary immensely in degree and character. One of the severe types constitutes the syndrome described here as eczema herpeticum.

Summary and Conclusions

Primary infection with the virus of herpes simplex, complicating infantile eczema, is probably often unrecognized although clinical diagnosis is possible. Two infants so affected are described, and attention is drawn to the characteristic features. Vaccination, and its bearing upon eczema vaccinatum, are commented upon. One case of eczema vaccinatum is reported. Despite the Lilliputian proportion of the present series, but in conjunction with the observations of others, the following conclusions suggest themselves:

The term "Kaposi's varicelliform eruption" should be discarded. Eczema herpeticum is suggested for extensive herpes simplex complicating eczema. It represents an exaggerated response to primary infection, and is highly infectious to susceptible persons. The primary inoculation of the virus may be via the damaged skin. Subsequent dissemination is haematogenous, with localization in the damaged areas. The prognosis is variable, but may be influenced by prompt diagnosis and prevention of secondary infection. Patients affected should be rigidly isolated. Persons afflicted with atopic eczema should be safeguarded from herpetic and vaccinial contacts, including members of the medical and nursing staffs if affected. Vaccination should never be performed in the presence of any skin damage, especially atopic eczema. It is doubtful whether the parents of children so afflicted should be vaccinated. If so, the vaccination site should be carefully occluded. Finally, both eczema herpeticum and eczema vaccinatum should be regarded as notifiable diseases.

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THE ADRENAL RESPONSE TO CORTICOTROPHIN

EFFECT OF A.C.T.H. ON PLASMA ADRENAL STEROID LEVELS

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In certain diseases corticotrophin (A.C.T.H.) is used as a therapeutic agent with the object of reversing or modifying the underlying pathological process by increasing the secretion of adrenocortical steroids. The hormone is injected intramuscularly or intravenously, the amount given being increased or reduced according to the clinical response, which varies widely in different patients. For example, Kellgren *et al.* (1952) observed that, whereas in one patient intramuscular A.C.T.H. might relieve the symptoms and signs of rheumatoid arthritis and induce metabolic changes indicating hypercorticism, in another patient presenting a somewhat similar clinical picture the same treatment failed to produce any clinical improvement or metabolic changes. They noted that some patients showed excellent clinical improvement when given cortisone by mouth but derived little benefit from intramuscular A.C.T.H. All the cases which responded to either A.C.T.H. or cortisone showed an eosinopenia, which suggests that in these a significant increase in circulating adrenocortical hormones had been achieved.

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In the present investigation the effectiveness of A.C.T.H. as an adrenal stimulus has been assessed by estimating the concentration of adrenocortical steroids in peripheral blood.

Materials and Methods

Adrenocortical hormones were estimated by a method which is relatively specific for 17:21-dihydroxy-20-ketosteroids such as hydrocortisone, cortisone, and their metabolic reduction products (Nelson and Samuels, 1952; Bayliss and Steinbeck, 1953). The volume of plasma required for each estimation has limited the number of determinations made in each patient. The mean value for isolated determinations in normal subjects by our method is 9.5 μg. of 17-hydroxycorticosteroids per 100 ml. plasma with 95% fiducial limits of 3 to 16 μg. The accuracy of the method is such that a difference of 3.3 μg. per 100 ml. between samples is significant.

Ordinary A.C.T.H. (Armour) and a long-acting preparation of A.C.T.H. in gelatin and propylene glycol ("acthar gel") were used in this investigation.

Results with Intravenous A.C.T.H. (Table I)

A.C.T.H. dissolved in saline was infused intravenously at as constant a rate as possible, the concentration being arranged so that the amount given per hour was contained in 100 ml. of saline. When the response to different doses or different batches of A.C.T.H. was determined in the same patient, an interval of at least three days was allowed to elapse between each infusion to avoid producing adrenal hypertrophy. When the response to repeated stimulation with A.C.T.H. was investigated the infusions were given daily.

Of the twelve patients only two were not clinically ill at the time of study, Case 7 being a normal control and Case 8 being referred as a case of Addison's disease, a diagnosis which was not confirmed. Of the ill patients, No. 6 had been in status asthmaticus for five days when given his first infusion, but was asymptomatic when given the second a week later.

A slight increase in the plasma level of 17-hydroxycorticosteroids was detected within 15 to 30 minutes of starting the infusion, and a definite increase had occurred within an hour (Cases 1 to 5). The levels after two hours were not very different from those at one hour, and thereafter remained constant for six hours in Case 1, but rose still higher in Case 4. When the infusion was continued for six or eight hours there was no consistent rise after the fourth hour (Cases 7 to 9). On stopping the infusion the steroid level remained high for an hour and then fell, returning towards the control value within three hours (Case 4).

The effect of different doses of A.C.T.H. given at intervals of at least three days was studied in Cases 8 to 11. In Case 8 there was little difference in the degree of steroid elevation induced by 0.25 and 2.5 units per hour for eight hours, and in Case 9 after eight hours the effect of 2.5 and 5 units per hour was the same, but 0.25 unit produced a smaller rise. Cases 10 and 11 were given repeated six-hour infusions of A.C.T.H in doses ranging from 0 to 3.3 units per hour. The results for Case 10 (Fig. 1) suggest that a dose of about 1 unit per hour caused maximum adrenal stimulation. (The poor response when 1.8 units was infused was probably related to difficulties in maintaining the drip at a constant rate during this particular infusion.) In Case 11 maximum stimulation was obtained with a dose of about 0.7 unit per hour.

Infusions of A.C.T.H., repeated daily, produced after six or eight hours a progressive rise in the steroid level, suggesting that repeated daily stimulation increased the hormonal output from the adrenal glands (Cases 3B, 3C, 12A, and 12B).

No significant difference was observed in the response to different batches of A.C.T.H. in Cases 6 and 7. The dosage