acting insulin—to be injected, let us suppose, once a week—could ever be successful; it would cause hypoglycaemia every night, and the patient's condition would be comparable to the rare syndrome of spontaneous hypoglycaemia. It is clear that the basal dose must be "tailing off" in strength of action at night.

Summary

1. The chemical nature and physiological action of zinc protamine insulin is described.

2. We have used it as one dose a day, from 16 to 50 units, in forty-two insulin patients of all grades of severity. In all cases the urine passed twenty-four hours afterwards can be made sugar-free and the blood sugar normal or nearly so. In many severe cases hyperglycaemia and glycosuria after carbohydrate meals, especially breakfast, cannot be controlled by such a dose of zinc protamine insulin alone, but can be better regulated by the addition of a suitable dose of soluble insulin injected in the same syringe.

3. The adjustment of diet, the dosage of insulin, and the possibility and prevention of hypoglycaemia are discussed. We consider that careful study of each case is essential.

4. We conclude, so far as our limited experience goes, that most severe diabetes can be well controlled and the patient maintained in excellent health by one injection a day, either of zinc protamine insulin suspension alone or with the addition of some soluble insulin. The initial stages of such treatment should be carried out under close observation.

We wish to thank our patients for their keen co-operation, and the nursing staff and the dietetic and laboratory staff in our department for loyal assistance in the extra work which these studies have required. We are indebted to Professor Best of Toronto for our first supply of zinc protamine insulin, and to Messrs. Boots Pure Drug Co. Ltd., who have supplied large quantities free since November, 1936.

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M. Schubert (*Derm. Wschr.*, December 19, 1936, p. 1653) believes with Miescher, Musger, and Kogoj that lichen sclerosus atrophicus represents an idiopathic affection, having the following characteristics: some spots are rounded or polygonal, of irregular but well-defined outlines. Their colour is bluish-white. They are either of the same level as the surrounding skin or slightly prominent or inversely slightly sunk. The surrounding skin is not red, but may show a slightly pigmented ring. Some of the spots develop into verrucous foci of grey-brownish colour with more or less extensive whitish margins. Small spots may coalesce to form large irregular but well-delimited foci of the colour of porcelain. There are also sunk, smooth, white, rounded scars with fine telangiectases. The affection can be distinguished both clinically and histologically from lichen ruber planus and from the circumscribed scleroderma, although there are transitional forms between lichen sclerosus atrophicus and the last-named two affections. The author prefers to call the disease "lichen sclerosus atrophicus" rather than "white spot disease" (Weissflecken Krankheit).

THE NOCIFENSOR SYSTEM OF NERVES AND ITS REACTIONS *

BY

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LECTURE II

The three reactions described in the first lecture were all discovered by observations carried out exclusively upon human subjects. The fourth, to which I now come, was first described in animals, and has been submitted to close experimental investigation in these.

4. The "Antidromic" Flush

The first definite statement of vasodilator nerves in the posterior roots was made by Stricker in 1876. But his observations remained unaccepted until Bayliss's careful experiments were recorded in 1901. Bayliss (1900-2) found that stimulation of the distal ends of the cut posterior roots by current, or mechanically, produces a long-lasting vasodilatation of the limb supplied. He showed that the cell stations of the fibres conducting the impulses to the vessels lie in the posterior root ganglia, for the effect remains after the posterior roots are cut, but is lost after the ganglia are excised. He concluded that the fibres concerned are the ordinary sensory afferent fibres of the posterior roots and that vasodilatation of the limb is effected by "antidromic" conduction, as he called it at Langley's suggestion. Similar vasodilatation can be produced by stimulating the distal ends of nerves to the limbs or cutaneous nerves, and these reactions have been studied by Langley (1923-4) and by myself and others (Lewis and Marvin, 1927), mainly in the cat's paw. Foerster has shown in recent years that reddening of the human skin over appropriate segments occurs when the posterior roots, or nerves of the limb running to the skin, have been cut and are stimulated distally. In the case of the cat stimulation of a small nerve of the paw flushes the bare surfaces of those pads which the particular nerve supplies, and flushes them sharply to a boundary. Langley first observed this, and, adopting my method of identifying active capillary dilatation, found that the flushing is produced even during circulatory arrest. He therefore, and rightly, concluded that the flush is due to capillary rather than to arteriolar dilatation in this animal.

The conception that the vasodilatation is due to antidromic conduction in sensory nerve fibres was grounded upon the contemporary belief that all posterior root fibres are afferent. Several workers (Ranson, Kuré, Tower) have since described intact fibres in the spinal ends of the cut posterior roots many days after section. These have been much discussed, and have generally been regarded as regenerated from the root ganglion. But Kahr and Sheehan (1933) traced intact fibres in this root after removing the ganglia; and Barron and Matthews (1934-5) have recently supplied some remarkable evidence, both physiological and anatomical, that fibres having their cell stations in the posterior root ganglia pass into the cord and send collaterals out again through neighbouring posterior roots on their way to the periphery. It seems from the observations of Matthews that these fibres normally carry impulses out to the periphery; but if that is so then it is difficult to regard the system of nerves in question as subserving a sensory function. Thus the evidence from this source inclines us to recognize that there are fibres other than sensory in the posterior

* The Hume Lectures delivered at Newcastle-on-Tyne, February 4 and 11. Lecture I was published last week.

root system, and in this respect it is harmonious with what has been concluded in earlier parts of these lectures. Although the posterior root's constitution is being closely re-examined by physiologists, and especially in relation to what has hitherto been called "antidromic" conduction, we do not yet know quite certainly that vasodilatation is ever provoked naturally through posterior root channels; neither are the fibres that give this response to artificial stimulation positively identified.

The idea that the vascular dilatation under discussion results from the release of an appropriate substance peripherally was first put forward on a definite basis by Marvin and myself in 1927. Langley apparently first suggested to Bayliss that such a substance may be released; but as there was then no tangible evidence for such release Bayliss considered it unfavourably. Langley recorded his idea later (1923), though I have been unable to ascertain what prompted him, unless it was his conclusion that the effect is capillary rather than arteriolar. The idea came to Marvin and myself independently when we noticed the long delay in the appearance and disappearance of the vascular reaction in response to short stimulation in cats, for these time relations reminded us of those of the flare in response to local injury. We sought for a means of testing the matter crucially and found it in arrest of the circulation, which by holding the released substance in place prolongs the reaction by just that period of time over which the blood flow is arrested. This experiment not only gave us evidence of a released substance but showed this substance to be relatively stable. We regarded the substance responsible for flushing of the pads of the cat's foot as a histamine-like substance acting upon the minute vessels of the skin. A few years later Kibjakow (1931) reported vasodilator substance in blood returning from a paw during distal stimulation of the posterior roots, but his evidence was unconvincing. More recently Ungar and his associates (1935) have found similar stimulation to result in increased secretion of hydrochloric acid in the stomach, a well-known effect of introducing histamine into the circulation. To these observations, which indicate histamine release, Wybauw (1936) has quite recently added others strongly supporting the view, first inferred by Dale and Gaddum in 1930, that there is a release of another natural vasodilator substance—namely, acetylcholine. Thus it becomes possible, if not probable, that there is a twofold release, H-substance playing upon and directly dilating the capillaries, and acetylcholine acting upon and dilating the arterioles.

I emphasize these peculiar effector reactions because they tend in themselves to separate the nerves concerned from the sensory system and to place them in the category of those of the nocifensor system, which are known or are suspected to produce their effects through the intermediary of cutaneous cell products.

General Hypothesis of "Nocifensor" Nerve Effects

In earlier parts of these lectures I have described, first, how hyperalgesia spreads around a local injury; and secondly, how similar hyperalgesia appears in the territory of a cutaneous nerve stimulated distally. Thirdly, I have redescribed the chief phenomena of the flare produced around a local injury; and fourthly, the vasodilatation following distal stimulation of posterior nerve roots or cutaneous nerves.

When we view all these four together they appear linked, for each reaction of hyperalgesia seems to have its vascular counterpart. The two reactions of hyperalgesia clearly employ an identical effector mechanism; the third employs the same or a closely related mechanism. All

these three employ nerves of the posterior root system, but not sensory constituents; the fourth also concerns nerves of the posterior root, but nerves which we begin to regard as probably not sensory. The term "nocifensor" was first applied to the first two reactions; I widen it to include the third reaction, the "flare." This widening of definition means perhaps that we must recognize fibres of separate function within one special system. The inclusion of the fourth reaction, despite seeming close linkage, should, I think, still wait on time and further observations. It is the least solidly established within the nocifensor group. Difficult as it may be to believe that it is not of the same category, some evidence remains which makes its inclusion uncertain. When both posterior root vasodilatation and "flare" were thought to depend on sensory nerves, one system for the two reactions was a natural conception; but the identity of the nerves underlying these two reactions has not been proved.

Vasodilatation from nerve trunk stimulation in the cat's paw is largely a minute vessel effect, and this is associated with release of a stable vasodilator (histamine-like) substance. No evidence has been found that the capillaries play an active part in the flare phenomenon, though it has been sought closely and repeatedly. And, consistently, none has been found that stable vasodilator substances are released in the flushed skin; on the other hand, the evidence is opposed to such release.* It may be that this difference in the type of vascular reaction has been found because the reactions have been studied in cat and man respectively, and are not strictly comparable. On the other hand, the difference may be fundamental. A second seeming disagreement is found between the characteristics of the nerves; for whereas I find the flare reaction abolished in relatively early stages of asphyxia, and at a time when slow-conducting nerves of the skin are still functioning, Hinsey and Gasser (1930) associated the vasodilatation of posterior root stimulation particularly with the slow-conducting fibres.

5. Reaction to Cold

There is a vascular reaction, certainly related to those already described, and one of obvious importance in defence. I discovered this reaction while investigating the sensation of warmth that develops in the fingers when they recover from handling snow (Lewis, 1930). If a single finger is immersed in ice-cold water, kept there for five or ten minutes, and then withdrawn, this finger warms up very rapidly and becomes even hotter than its fellows. Investigation shows that the vasodilatation happens while the finger is actually exposed to cold. The finger in its cold bath is at first painful, but after a time the pain, and even the sense of coldness, vanishes. A thermal junction strapped to the end of the finger shows at this time that the temperature has ceased to fall and is beginning to rise. So great is the fully developed vasodilatation that the thermal junction may show a rise of 5° or 10° C. (9° or 18° F.) above its low point of cooling while the finger still remains immersed in ice-cold water. The reaction lasts ten to thirty minutes and subsides, the finger cools again, and the events are repeated. Thus the immersed finger is kept at a temperature in the average well above freezing-point. To display the reaction it is unnecessary to cool to this degree; immersion at 5° or 10° C. (41° or 50° F.) provides quite obvious reactions, and there is a distinguishable response when cooling goes no lower than 15° C. (59° F.) or even 18° C. (64° F.).

* It is to be stated that the evidence referred to (Lewis, Grant, and Marvin, 1927) does not exclude the release of an unstable substance such as acetylcholine, but here this is not the precisely relevant point.

These reactions are not confined to experiments arranged within doors; they occur naturally in cold weather out of doors. In walking out of doors in cold air, or in working with hands in cold water, it is usual for the temperature of unprotected hands to fall almost to that of their surroundings. But they do not remain cold in healthy people; when they have cooled to a certain point, which may be reached in a half-hour or more, they react and become warm again. It is clear, from the range of provocative temperature, that the reaction must come into very frequent play during the colder months of the year in northern climates. The importance of this reaction as a protective mechanism against prolonged overcooling is emphasized by considering the remaining responses to cold. When the surface of the body is cooled general vasomotor tone increases; at the same time the digital arteries respond directly to the cold by contracting; this contraction, by lessening blood supply, exposes the finger to further loss of heat and to further constriction of its vessels. Thus these two factors, acting alone, would inevitably bring about advanced and stable arterial spasm; such spasm is avoided or is relieved by the intervention of the reaction here described.

The reaction is found in the fingers and toes, the palms and soles, the lobe of the ear, the nose, and the chin. It seems to be especially well provided for just where it is wanted—namely, in parts of the body that project, have large surfaces, and are easily cooled. It is most conspicuous in the digits, which cool more than any other part, and these are richly provided with arterio-venous anastomoses, which vigorously participate in the response (Grant and Bland, 1929-31). I have recorded the reaction in the cat's paw, and Grant has studied it in the feet of birds and ears of rabbits.

The underlying mechanism is nervous. The reaction occurs in man after section of the mixed nerve to the skin up till the time of its degeneration, but not afterwards; and it is present after sympathetic degeneration. Thus the reaction happens as a local axon reflex in nerves belonging to the posterior root system, like those previously described. This conclusion, which I arrived at from my original observations upon human fingers, has been confirmed recently by Wybauw for the cat's paw (1936); the reaction is maintained after posterior root section, but is lost when, after ganglionectomy, the nerves degenerate. From my earliest interest in this subject, more than seven years ago, I took the view that the mechanism constitutes an important contributory means by which the temperature of exposed parts is normally maintained and the skin guarded against seriously injurious cooling; and that the fall of temperature of fingers deprived of their mixed nerve supply, as in injuries of peripheral nerves, is due to the loss of this local reflex. This view has been corroborated by later observations, many of which have been published with Dr. Pickering (Lewis and Pickering, 1936), and quite recently by Wybauw, who finds that the cat's foot deprived of nerves of the posterior root system by ganglionectomy (ensuring degeneration) becomes habitually lower in temperature than the foot to which the roots have been cut proximally to the ganglia.

In my earliest account of it I took the view that the reaction described is comparable to the "flare," and regarded the stimulus to the reaction as the same as that arising in acute injuries of the skin—namely, the release of H-substance. But there have been minor objections to the view that the reaction is equivalent to that occurring in the triple response (Grant, Bland, and Camp, 1931-3). There is no doubt in my mind that the stimulus cold injures the skin and releases a substance, but this

substance is not necessarily the histamine-like substance which underlies the "flare." There is also no doubt that in ice-cooling the nocifensor nerves are stimulated. The finger which has been immersed and reacts becomes hyperalgesic, and this hyperalgesia spreads in susceptible subjects, and, when the finger is the fifth, to the whole cutaneous area of the ulnar nerve. A vascular reaction has never been detected, however, beyond the limits of the finger cooled. The proved nocifensor element in the reaction is hyperalgesia; the associated vascular reaction may be comparable to that of the "flare," or it may be more akin to that which has been termed "antidromic," assuming the two last to be really separate. Thus it will be gathered that the vascular reaction to cold, like those previously described, is probably to be reckoned among "nocifensor" reactions, though its precise relation to the remainder has not yet been determined.

It is tempting to bring all the five reactions described unhesitatingly together and definitely to ascribe them all to the same system of nerves; such an idea has indeed very much to support it, but the conclusion cannot be drawn in the present state of our knowledge with the finality that we might desire.

Trophic Nerves

It is desirable to refer briefly in these lectures to the old hypothesis of "trophic nerves."

The term "trophic change" was introduced to imply a change of nutrition. Early in the nineteenth century emphasis was laid upon the control of nutrition by the nervous system and upon the possibility of lesions arising out of disease of the brain or spinal cord. Thus in 1831 Mitchell was attributing acute joint trouble to irritation of the spinal cord. By the time Charcot (1872-3) gave his well-known lecture on disorders of nutrition, and largely as a result of his work, the idea had taken fast hold; as he said, "there is nothing better established in pathology . . . than the existence of trophic troubles consecutive to lesions of the nervous centres or of the nerves." The truth of this statement is no less obvious to-day than in 1872 when it was written. When a motor nerve is cut the muscle atrophies; when the nerve to a secreting gland is cut the gland changes. Disuse, acting directly, and diminished blood supply, whether primarily the result of a nerve lesion or as so often happens itself the result of disuse, are two common and well-recognized channels through which nervous diseases cause trophic change, using the term in its literal sense of nutritional change. Relevant examples are many, but they are diverse. If we allow the word trophic a wider meaning, and include inflammation, then we may cite as further examples of neurotrophic lesions such ulcerations of eye or foot as can be attributed partly or wholly to insensitiveness of the corresponding structures and to injury arising therefrom. Sherrington (1900) aptly said "that every nerve and nerve centre that can influence the proper and specific activity of a tissue—and that is the sole function of nerves—possesses, in so far, a trophic influence on that tissue. If by trophic nerve be understood no more than this, all nerves are trophic nerves."

But more than this has often been inferred or implicitly stated. A notable instance was that of Claude Bernard (1852), who at first misinterpreted the function of the cervical sympathetic, regarding it as controlling metabolism, but abandoned the view when Brown-Séquard and he recognized its vasomotor function. The hypothesis of special "trophic nerves" came from Samuel in 1860. He believed in nerves *sui generis*, directly influencing nutrition, growth, and new cell formation, and

capable also of provoking inflammation. He ascribed separate effects to their paralysis and to their stimulation, and brought an array of experimental and clinical evidence into support of his views. His experiments though numerous were crude, and possess little value to-day. On the clinical side he cited many previous reports, and followed Brown-Séquard's view (1859) that herpetic eruptions after nerve injuries are irritative and Baerunsprung's attribution of zoster to affection of the spinal ganglia. Tangible evidence for the existence of a distinct system of nerves having the functions he ascribed to them is not to be discovered in his book, and his hypothesis rightly won little credence; there has been no reason to believe that nerves influence the nutrition or growth of tissue directly, but only indirectly by altering blood flow or by controlling the tissue's specific function. But although Samuel's hypothesis failed he was right in stressing as unexplained the apparent effects of nerve irritation. The mystery of the cases that have come to be called "causalgia" has remained; when Brown-Séquard concluded such lesions to be the result of irritation he may have been correct, but this fails to satisfy. Samuel's suggestion that they result from the excessive action of his special nerves of nutrition, an overaction exploding in inflammation, was not grounded on proper evidence; but it contained an element of truth. For according to our present evidence distal stimulation of cutaneous nerves does provoke some of the phenomena of inflammation—namely, hyperalgesia and reddening—and may conceivably provoke more. And it is of further interest to remark that while we cannot follow Samuel in regarding the nerves involved as special nerves of nutrition, we are coming to regard them as nerves exercising a special function, termed for convenience "nocifensor."

Conclusion

We have concluded that a specific system of nerves, connecting to at least the skin, exists. This system of nerves is capable of effecting changes in the skin locally and without reference to the central nervous system, though very possibly also capable of excitation from brain or cord. In speculating about the mode of action of these nocifensor nerves with a view to presenting a fuller if more hypothetical conception of them we might venture to suppose that they are nerves exercising no direct influence upon the nutrition of the skin but comprising in their actions an influence more akin to a process of secretion—and in parenthesis it is interesting to note that Charcot inclined to interpret Samuel's ideas in a similar sense. We might regard the nerves as liberating potent substances from cellular elements of the skin into surrounding spaces, and thus controlling partly or wholly within the skin important elements of defence, including inflammation.

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ACTIVE IMMUNIZATION AGAINST TETANUS

BY

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Passive immunization against tetanus was used with considerable success during the great war. In October, 1914, there were thirty-two cases of tetanus per 1,000 of the wounded admitted to the hospitals in England, but in November, after the general adoption of passive immunization of the wounded, the incidence fell to 1.7 per 1,000, and among those cases which did occur the mortality was lower.

Objections to Passive Immunization

Passive immunization, however, has serious disadvantages. Antitoxin, to produce the best effect, should be injected within twenty-four hours of sustaining the injury; this, for several reasons, may in many cases be impracticable. Another disadvantage is that antitoxin from the introduction of a foreign serum quickly begins to disappear from the circulation, and within a fortnight is no longer in sufficient concentration to afford protection; the injection has to be repeated at weekly intervals and before any subsequent operation is undertaken, since tetanus bacilli or spores may remain latent in the tissues for a long time.

Another serious drawback is the sensitization to horse serum, which to a greater or less degree follows immunization with antitoxin derived from immunized horses, a sensitization continuing for many years. Troublesome serum reactions, and even severe and in some cases fatal anaphylactic shock, may accompany or follow the subsequent injection of a therapeutic serum which may be urgently required in the treatment of an infection such as diphtheria.

Sensitization also considerably diminishes the immunizing effect of a further injection of serum. Glenny and Hopkins (1922) found that while in the case of a normal rabbit the titre of antitoxin in the blood dropped to a low level in twelve days after the intravenous injection of antitoxic horse serum, in the case of a rabbit sensitized to horse serum the same low level was reached in four days. Kahn and McDermott (1934) found that while the injection of 5 units of diphtheria antitoxin could protect a normal rabbit against fifty minimum lethal doses of diphtheria toxin, 75 units were required when the animal was sensitized to horse serum.

Tetanus Toxoid

Active immunization by tetanus toxoid has none of these disadvantages. There is no more difficulty in immunizing against tetanus than against diphtheria; it is quite free from danger and the result is just as satisfactory. Complete and permanent immunity is obtainable. A commission to study the question of prophylaxis against tetanus in the French Army strongly recom-