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THE NOCIFENSOR SYSTEM OF NERVES AND ITS REACTIONS*

BY

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LECTURE I

In these lectures I propose first of all to give an account of some recent discoveries of fact which have led me to believe that the superficies of the human body, including skin and mucous membrane, is supplied by a hitherto unsuspected system of nerves, subserving a special function. The nerves are distinct from those conveying sensory impulses, though, like the latter, they are comprised in the posterior root system. I shall begin by describing briefly the chief observations and experiments†, which were directly responsible for these conclusions—evidence for a "nocifensor" system of nerves, as I have termed it—and shall then proceed to discuss the relation of the reactions displayed to other reactions that have been recognized previously in skin.

1. Spreading Hyperalgesia from Local Injury

It is well known that when skin is injured locally tenderness develops. This is common to all subjects and to all kinds of injury, provided that these are sufficiently severe and extensive. But in many people tenderness develops readily, even when the area of injury is quite small, as when a minute fold of skin is gripped and crushed by the points of a forceps, and the tenderness is found not only at the site of injury but as a delayed effect in a more or less widespread area of surrounding skin. I must emphasize the fact that this tenderness around an area of local injury varies much in its degree and in its extent in different subjects. Thus a tiny crush of the skin may yield in some no recognizable hyperalgesia, in others it is sufficient to produce tenderness over a considerable area of skin. It will be understood that subjects in whom this outlying tenderness is displayed in response to quite small injuries and in whom the tenderness is readily detected and widespread are alone suitable for demonstrating the reactions to be described.

Crushing the skin is perhaps the most convenient form of injury to employ, because it is effected so easily and so quickly, is so readily confined to a tiny area, and is yet severe in its degree. A tiny crush of the skin of the forearm in suitable subjects causes the development of a small area of surrounding hyperalgesia within a few seconds, and this area gradually spreads to become full in about ten to twenty minutes. The full area is oval, is in the length of the forearm, and may be as long as 5 to 20 cm. (Fig. 1). It lasts for several or many hours.

The hyperalgesia is not primarily caused by the effect of painful impulses on the central nervous system; that is to say, it is not referred from the brain or spinal cord. Let a small cutaneous nerve of the forearm, such as the anterior branch of the external cutaneous be anaesthetized by injecting 1/2 to 1 c.cm. of novocain in the immediate neighbourhood of its stem, and the injury then be made in the centre of the affected area when the skin is fully anaesthetic and analgesic. The crush is unfelt; nevertheless, as soon as the nerve recovers, the usual area of hyperalgesia is found around the injury. It arises through a local mechanism, and this mechanism is nervous. This is suggested by the observation that if the injury has been made near the centre of the territory of a small cutaneous nerve, as ascertained by anaesthetizing the latter, the area of hyperalgesia subsequently developing will be found to occupy a closely corresponding area of skin. It is proved

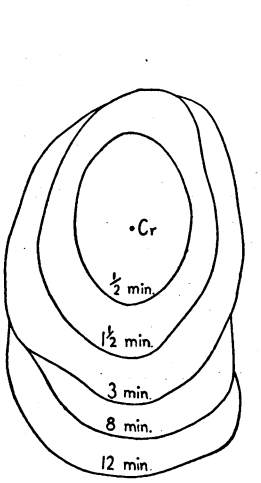

FIG. 1.

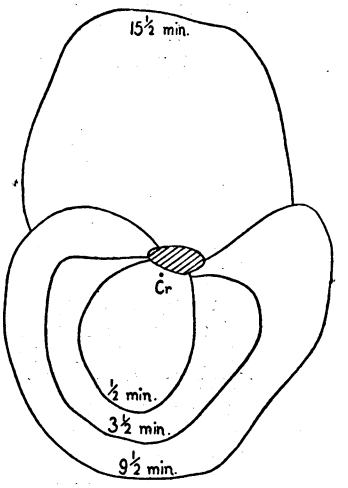

FIG. 2.

FIG. 1.—Half natural size. A tiny fold of skin was picked up in the points of forceps and crushed at Cr. Hyperalgesia was mapped out as it developed in the surrounding skin; the contours are marked with the corresponding times in minutes.

FIG. 2.—Half natural size. An area of skin was anaesthetized (shaded area) with 1 per cent. novocain to act as a barrier. A tiny fold of skin (Cr) was crushed. Hyperalgesia was mapped out as it developed; the contours are marked with the corresponding times in minutes. The anaesthetic barrier recovered between nine and a half and fifteen and a half minutes.

* The George Halliburton Hume Lectures delivered at Newcastle-on-Tyne, February 4 and 11, 1937.

† A full account will be found in my original article in *Clinical Science*, 1936, vol. 2, p. 373.

by using local cutaneous anaesthesia. The skin is injected intradermally with novocain; and the crush is made painlessly upon the centre of the small insensitive wheal of novocain. Surrounding hyperalgesia does not develop in these circumstances. The skin may recover sensation ten minutes or an hour after its injection, according to whether adrenaline has been introduced with the novocain or not; as it recovers, early or late, the usual hyperalgesia appears in the surrounding skin.

This experiment is important from two points of view. First, the failure of hyperalgesia to appear while the local anaesthetic holds shows that hyperalgesia, when it occurs, is not due to the spread of a pain-producing substance, which might be conceived to be released at the site of injury and to spread out into the surrounding skin; it shows that the action depends on the functional integrity of the nerves of the skin. Secondly, the development of surrounding hyperalgesia, as the area of crush recovers sensitivity, demonstrates that the capacity to provoke distant hyperalgesia resides in and is maintained by the crushed skin; the products of injury, so it may be conceived, act through local nerve channels as soon as these become unblocked. The products of injury, and not the pain of injury, are responsible, for as we have now repeatedly seen pain may be eliminated by blocking the nerves without affecting the reaction. Further, the unanaesthetized skin may be injured painlessly, as by suitably freezing it, and yet the result is the same. That tissue products of injury are responsible is also supported by the fact that the time at which hyperalgesia develops depends on the intensity of injury; the time is shortest when the skin is smashed; it is long when the skin cells are injured but not killed, as when a faradic current or freezing is employed. It is to be emphasized that the action happens through purely local nerve channels; the central nervous system is not concerned in this. It is a reaction explicable only on the basis of what has been termed an "axon reflex," the impulse travelling up a nerve fibre and returning shortly through a side branch.

We may proceed further to consider the arrangement and kind of nerve fibres that are involved. When hyperalgesia fills a large territory in response to injury confined to a central and quite small injury it is clear that, if we conclude hyperalgesia to be provoked through local nervous channels, the small area of injury must be connected by nerve paths to all parts of the large territory. Thus we are brought to believe that the nerves under consideration are nerves the axons of which divide freely to form arborizations or networks in the skin. Further observations support this idea. It has been stated that, when a tiny piece of skin is crushed in the centre of a small circular area of skin anaesthetized by intradermal injection of novocain, hyperalgesia appears only when the anaesthesia recedes and exposes the crush. If the injury is made eccentrically then it becomes exposed earlier during the recovery and while the skin still remains anaesthetic on one side of it. Under these conditions the hyperalgesia appears early on the side of exposure; it fails to appear on the other side until the intervening barrier of anaesthesia has recovered. Similarly, if the skin is crushed quite near to a barrier of locally anaesthetized skin (Fig. 2), hyperalgesia develops, but again it fails to pass beyond the barrier. Crush the skin a little farther away and the hyperalgesia in this case tends to creep around the barrier. Observations of this kind indicate that the nerves through which the reaction develops lie largely in the skin itself, and seem to indicate that the fibres concerned belong to complex and overlapping arborizations rather than to networks.

Hyperalgesia of the kind discussed is the ultimate result of a reduction in the threshold of sensory nerves subserving pain; but while this is to be accepted it should not mislead us into believing that the nerves through which the local state underlying hyperalgesia is provoked are pain nerves. Consideration, indeed, shows that this cannot be so. The nerve fibres primarily involved in provoking the reaction are freely arborizing. Accurate localization of painful stimuli, such as we know exists, could not be effected through a system of this kind, for impulses travelling from widely separated end-branches of a given arborization would each finally travel by the same path and produce an identical effect upon the central nervous system. An additional argument against nerves of pain being involved is that the nerves underlying the production of spreading hyperalgesia in response to local injury are very readily thrown out of action by asphyxiating them, while the pain nerves are much more resistant (unpublished observations). It is clear, therefore, that the pain nerves are concerned merely in registering an altered state of the tissues; and this altered state is produced through a distinct system of nerves. But the argument, derived from our ability to localize stimuli, applies not only to the pain impulse but to all other forms of cutaneous stimulation, namely, to touch, warmth, and cold; for all these sensory impressions are localized with accuracy, and none, therefore, can be subserved by a system of widely branching axons. Of known nerves there remain only the sympathetic fibres, sweat nerves, pilomotor nerves, and nerves supplying blood vessels. It is of interest to note that in the case of sympathetic nerves it has previously been concluded that freely branching axons having the required anatomical arrangement exist in skin; such has been proved for the pilomotor nerves (Lewis and Marvin, 1927). But observation shows quite conclusively that the sympathetic system is not concerned in the production of spreading hyperalgesia, which can be as easily provoked by small injuries in skin deprived of its sympathetic nerves as in normal skin; this has been tested in patients from whom the cervical sympathetic ganglia have been removed and the nerves to the tested skin of the arm have been allowed to degenerate. Now the sympathetic nerves and nerves of the posterior root system are the only nerves that supply skin; and complete destruction of the former leaves the reaction intact. Therefore the nerves we seek must belong to the posterior root system, though as we have seen they are not sensory nerves. Thus we are brought seriously to consider a system of nerves hitherto unrecognized. That the sensory and sympathetic nerves form the complete cutaneous supply is an idea for which there is in fact no sure foundation. We have come to recognize given systems of nerves by their manifestations; first, sensory nerves, because they were found to convey sensory impressions to the brain, and afterwards vasomotor, pilomotor, and sudorific nerves as changes in blood supply, erection of hairs, and sweating became recognized to be under the governance of nerve systems. It will be evident that any system of nerve fibres, which in the exercise of its function gives rise to no obvious and distinctive external manifestations, will tend to escape recognition. That is what has happened up to the present time in regard to the nerves now discussed. The present need to postulate a new system of nerves has arisen to explain hitherto unrecognized phenomena. Because the nerves in question are associated with local defence against injury I call them "nocifensor nerves." The defence that I have primarily in mind is the protective hyperalgesia that has been described; but I also have in mind the possibility of other protective reactions to be described.

I pass to the second reaction.

2. Hyperalgesia from Distal Stimulation of Cutaneous Nerves

Hyperalgesia of the skin can be provoked not only by injuring the skin locally but also by stimulating cutaneous nerve trunks. The nerve can be stimulated by faradic current either through the skin or preferably by introducing a small and special electrode through the skin. Such hyperalgesia is confined to and usually fills the territory of the corresponding nerve. The change produced in the affected skin is undoubtedly the same as that produced as a spreading response to local injury; the hyperalgesia has the same qualities, develops after delay and slowly, and lasts for correspondingly long periods of time. We may conclude without hesitation that in both instances the same special system of nerve fibres conveys impulses to the skin, though the impulses start from an area of injury in the one case, and directly from the nerve

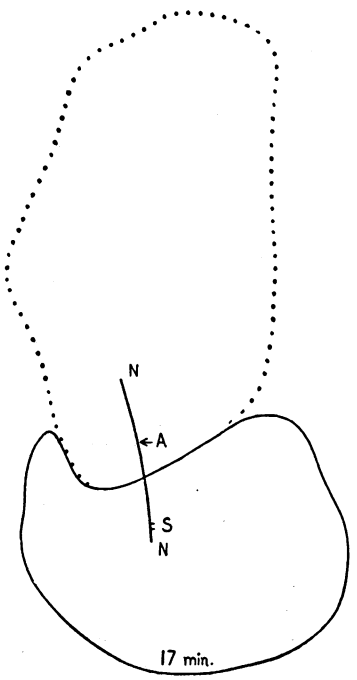

FIG. 3.

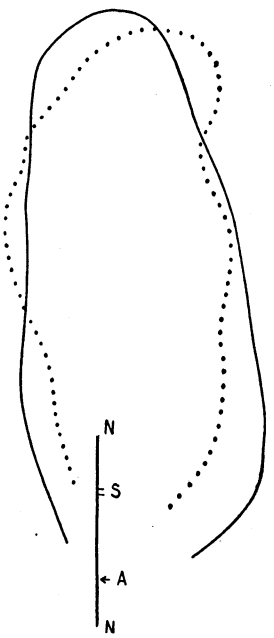

FIG. 4.

FIG. 3.—Half natural size. A subcutaneous nerve NN was anaesthetized at A by local injection of novocain; the area of defective sensibility resulting is mapped by the dotted line. The nerve was stimulated by faradic current passing through the skin into the nerve at S, proximal to the block. The only hyperalgesia subsequently developed is shown by the area mapped by the solid line at seventeen minutes. (From *Clinical Science*, 2, 386.)

FIG. 4.—Half natural size. The same nerve was anaesthetized at A and stimulated distal to the block at S. The area of hyperalgesia developed after the recovery of the block is mapped by the solid line. (From *Clinical Science*, 2, 386.)

trunk in the other. That the action in the case of nerve trunk stimulation is a distal one, and is not brought about through the conduction of impulses to the central nervous system, and by reflection or reference from this, may be proved in this instance also. If the nerve trunk is blocked by a little anaesthetic injected into it, and it is then stimulated above the block (Fig. 3), hyperalgesia does not develop subsequently in the nerve's territory, though the central nervous system receives the full sensory stimulus. But if stimulation is below the block (Fig. 4) it is painless, and when the block recovers the usual area of hyperalgesia is found. Thus the evidence is harmonious in showing that there is a common end-effect, a changed condition of the skin produced through a local and common effector mechanism.

It will be of interest briefly to discuss the nature of this change in the skin which is common to the two reactions described, though it cannot be said that we are more than beginning to understand it. When the skin is injured locally and surrounding hyperalgesia is allowed to develop, local anaesthetization of the damaged skin will not abolish the hyperalgesia, which continues unchanged under as much as an hour's observation. Once hyperalgesia has appeared it is maintained, although receipt of new impulses has been brought to an end through the blocking of the nervous channels issuing from the site of original injury; the change which has happened in the affected skin is a relatively stable affair. A precisely similar stability is shown in the case of the hyperalgesia provoked by direct nerve stimulation. In this instance there is no durable change at the point of nerve stimulation, which might be thought to maintain a state of hyperalgesia in the skin; for nothing develops in skin, which is guarded by peripheral nerve block over the actual period of nerve stimulation, when that block is released. It is again clear that the skin supplied by the nerve is itself the seat of disturbance and that the change that happens there is a lasting one. For reasons which I cannot satisfactorily and fully relate in these lectures I have interpreted this change (Lewis, 1936) to be an altered state of the skin cells, with a discharge from these of substances that, by acting locally, reduce the threshold of the pain nerves. In this connexion it is of interest to note that Foerster (1925) has recorded the occurrence of pain during distal stimulation of divided cutaneous nerves in man. On the lines already laid down I attribute his interesting observation to the release of pain-producing substance, which acts on overlapping endings of neighbouring sensory nerves, and find support for this view in Foerster's statement that section of these neighbouring nerves abolishes the pain.

While it is legitimate to conclude in my own observations that the hyperalgesia, accompanied as it often is by a little sense of burning, and the pain in Foerster's observation are both due to the onset of a new and relatively stable state in the affected skin, the view that this comprises a release of pain-producing substance must be recognized as more hypothetical. It will remain so until more direct evidence of actual release becomes available. That the nerves act by increasing the permeability of the walls of the cutaneous cells, and thus cause a release of substance or substances, is but one of several possible ideas which might plausibly be put forward in explanation. But it is the conception which at the moment I am most inclined to favour.

Clinical Applications

Before passing on to other reactions of the skin I pause to comment on certain practical clinical bearings of the observations that have been described. The first reaction, that of spreading hyperalgesia in response to local injury, is an event of everyday life. Such hyperalgesia is often to be found around abrasions and other small injuries of the skin, for example, those produced by insect bites. Areas of hyperalgesia, extending widely around inflammatory lesions of the skin, almost certainly arise through a similar mechanism. So does tenderness referred from stimulation or inflammation of the mucous membrane of the maxillary antrum (Fig. 5), or from teeth in the upper jaw, to skin in the territory of the maxillary nerve. Thus it is evident that the observations and experiments described bring a clear understanding of

many instances of superficial hyperalgesia such as are encountered in patients. As to whether or nor referred cutaneous tenderness from visceral disease employs the same effector mechanism will be decided by new investigations.

The second reaction, the production of hyperalgesia through stimulation of cutaneous nerves, finds its counterpart in certain cases of peripheral nerve lesion. The cases to which I refer are those relatively rare ones, examples of which were first recorded by Paget (1853), Charcot (1859), Weir Mitchell (1872), and others, in which as a result of bullet wounds or other injury the nerve in a limb (usually the median), though undivided is contused, or becomes involved in chronic inflammation. In such cases and after a notable latent period of a few or many days, the skin of the corresponding territory becomes exceedingly tender to friction and intolerant to warmth. The pain, like all continuous skin pains, is described as burning in quality—whence the term "causalgia"—and is so easily elicited and so severe when provoked that the patient guards the limb closely, holding it flexed and covered, and shrinking from all threatened contacts. Such cases have long been suspected to owe their suffering to

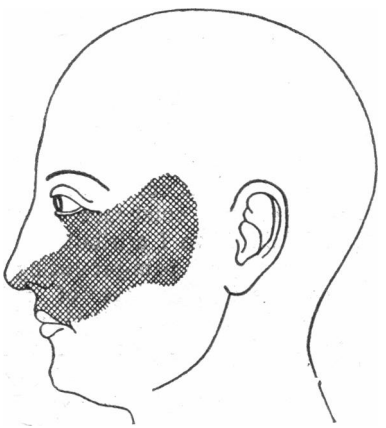

FIG. 5.—A diagram of hyperalgesia of the facial skin appearing within an hour of stimulating the mucous membrane of the outer wall of the maxillary antrum with a faradic current. Similar hyperalgesia appears with catarrh of the same antrum. (From *Clinical Science*, **2**, 393.)

irritation of the nerve trunks, sensory impulses being conveyed directly to the sensorium from the region of the wound. But my observations provide a definite basis for a new suggestion, namely, that the pain may arise from the irritation not of sensory but of "nocifensor" fibres in the nerve trunk. In the latter instance it would arise indirectly and after a period of delay, the state of the skin being changed and thus lowering the threshold of the pain nerves running to it. The existence of such a mechanism, the pain-provoking agency being in the skin and not in the nerve trunk, would explain those curious and otherwise inexplicable instances cited by Tinel (1918) in which section of the nerve distal to the nerve lesion has brought relief of pain. Another reason for suspecting an action of the damaged nerve distally is found in the associated changes in the skin, including reddening and herpetic eruption; but further discussion of this aspect of the question I shall defer to my second lecture.

Another type of case is that in which a finger has been crushed, torn, or otherwise injured, and in which, though healing occurs, similar intractable tenderness and pain develop and often spread to the adjoining finger. For these instances of reference to an adjoining finger it has become quite probable that the painful phenomena are produced through the intervention of nocifensor nerves; though it is to be stated that further observations directed to this question are desirable as opportunity offers.

We pass on to the third reaction.

3. Flare from Local Injury

The flare surrounding local injuries has been so fully described in my writings on the "triple response" that I shall here confine myself to what is relevant to the main thesis of these lectures. If a small piece of skin is crushed or is injured in any other way a vascular flare appears around it. This flare is due to the dilatation of the small arterioles in the skin over an area usually of about 5 cm. diameter, though sometimes visibly extending for much greater distances. It has been proved to occur through the intervention of a nervous reflex, the impulses travelling locally through branching axons of skin and directly underlying tissue. Thus the flare can be provoked after all nerves to the skin have been divided. It disappears when after section the fibres of the cutaneous nerves have had time to degenerate. It is lost when the posterior root ganglia (or the fifth nerve ganglion) have been destroyed; but it is not lost after degeneration of the sympathetic nerves to the skin has taken place. Thus the nerves underlying this reaction are known to belong to the posterior root system, and for this reason have been thought to be sensory. This latter view, based as it was on reasoning by exclusion, I am unable any longer to hold. The resemblance between the nervous mechanism of this reaction and that of spreading hyperalgesia is so close as to draw strong attention to itself. The reason for first suspecting the nerves underlying the hyperalgesia to be separate from any of the sensory nerves was that the phenomena displayed require for their explanation a branching system of axons, a system regarded as incompatible with accurate localization of sensation. A parallel argument applies in the case of the flare. The stimulus that provokes this flare arises locally; nerve impulses pass out from a small place of injury and travel to small cutaneous arterioles supplying the whole area flushed. Thus each small area of skin must be united through axonic nervous channels to all regions displaying vasodilatation. A branching system of axons, incompatible with the function of sensory localization, is again needed to explain this local reflex.

It is to be noted in the case both of flare and hyperalgesia that the original stimulus is a small local injury, like a crush, and that in each instance independent evidence has been obtained that the receptor endings of the nerves are stimulated by substance released. The paths taken by the nerves through the skin, as displayed by the effect of anaesthetic barriers, are remarkably similar in the two instances. Asphyxia affects both reactions early, though the flare is affected distinctly later than the hyperalgesia (unpublished observations). All this evidence leads us to conclude as in the case of hyperalgesia, so in the case of the flare, that the nerves concerned are not sensory, but that those underlying the two reactions are related to each other. But farther than this in identification we cannot go.

I have described the similarities that seem to me sufficient to allow us to place these nerves in a common system. There are also important differences. The substances released by (and at the point of) injury and responsible for the two reactions are different. The flare is caused by the release of a histamine-like substance; the substance causing hyperalgesia is certainly distinct. Again, the end manifestations are different in character and they are of very different duration. Each reaction may have its appropriate stimulus and receptor

mechanism, each may have its distinct effector mechanism ending, the one perhaps on skin cell and the other perhaps on arteriole. These possibilities are all in accord with the facts as these are known, and we should be justified, therefore, in regarding the two series of nerve paths as separate. The general conception would be similar to that which we take in the case of pilomotor and sudorific nerves. Here also are two series of nerves following similar branching axonic paths in the skin; but they arise differently, end in connexion with different cells, and produce for that reason dissimilar effects; but both belong to the same general system, the system of sympathetic nerves.

[A full List of References will be given at the conclusion of the second lecture.]

FOOD AND NUTRITION*

BY

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[In the opening part of his lecture Professor Cathcart gave a brief review of the food side of the problem in the light of present-day knowledge, stressing the great gaps in this knowledge that still exist.]

When we turn to the question of nutrition we enter a realm which is largely speculative. There are those who hold that the state of nutrition is definitely, and by inference only, an index of the adequacy of the diet. Personally, in common with many others, I believe the state of nutrition indicates much more than the adequacy of the diet.

We all believe that we can decide, with a certain degree of assurance, whether the state of nutrition of a given individual is good or not, and yet, at the same time, if we were asked to state why we reached our degree of certainty we would be hard put to it to give an explicit answer. In other words, we do realize that in this state there is something more involved than mere physical attributes like stature, bulk, bloom of skin, gloss of hair, and so on; that there are also intangible psychic factors which may be summarized in terms like "alertness," "fitness," "aliveness." We judge normally by the "wholeness" of the picture. It is a question of the primacy of the whole over the separate parts. We arrive at our assessment by a kind of intuition based on our own particular experience.

I have no doubts in my own mind that the term "nutrition" should be retained for a wide conception of the state of well-being which characterizes the individual who is both physically and psychically sound. Those who wish to refer only to the influence of food on the body, who, in other words, wish to limit their conception, would have quite a useful and sufficient word in *alimentation*. They could speak then of states of good and bad alimentation—that is, the states resulting from the ingestion of adequate or inadequate diets. If the words were not quite so exotic we might adopt, for differentiation, the words used by the Greeks—*eusitia* and *eutrophia*. I understand from my classical colleagues that the Greeks, more precise in the use of words than we are, differentiated between well-fed (eusitia) and well-nourished (eutrophia). These words have the additional advantage that a negative form dysitia and dystrophia may be used. I believe it must be accepted that when we speak of, say, excellent nutrition (eutrophia) and malnutrition (dystrophia) we are speaking of clinical syndromes, because in everyday practice it is found there is no physical yardstick by which the degree of nutrition can be measured. Moreover, every medical man realizes the extent to which physical conditions like weight can be dominated by psychical states, and how, for instance, an immobilized limb can atrophy despite an adequate food intake. It is quite clear to me at least that when we use that much-abused term "malnutrition" we are referring to a state of the body which is not solely dependent on the inadequacy of the food intake; that many other factors like lack of sleep, of play, of fresh air, of happiness, absence of worry, and so on play parts in the determination of the condition. It is admitted, of course, that an adequate supply of proper food is absolutely essential, but food alone cannot work miracles.

"Malnutrition"

I have stated that there is no measure by which the degree of "malnutrition" can be defined; hence it is not surprising that where each individual medical officer makes his own subjective judgement, a judgement which can be distorted by all manner of personal, but probably in the majority of cases unconscious, predilections, wide variance in the extent to which "malnutrition" is reported to exist in given areas is to be expected. Until some standard, some method, can be devised which will rule out these individual predilections no finality can be reached. It is not that the search for such a measure has been neglected. Repeated attacks have been made on the subject, and each time the examining committee has fallen back on the clinical findings.

The question of the extent of "malnutrition," be the cause what it may, has given rise in recent times to great debate, much of it extraordinarily ill informed. One of the greatest of statisticians in this country, Mr. Udny Yule, speaking recently on the fall which had taken place in the death rate, said:

> "That such a change must mean a very great improvement in the condition of the poorer part of our population, which forms the great majority of it, seems to me obvious, and I think this cheering story deserves some special emphasis at present, when there is much talk, some of it sensible but some of it a bit lurid, and some of it—I think it is hardly too much to say—a little hysterical, on such matters as housing, unemployment, and nutrition. Some of it indeed is to me almost incredible, for if any large proportion of our population be as seriously undernourished as it is sometimes represented the existence of such low death rates becomes difficult to explain, and if unemployment were as grave a factor as is sometimes alleged it would be odd that unexampled unemployment should be accompanied by record low mortalities."

This comment receives support from the evidence collected by school medical officers, which, despite its variable quality, does not disclose the existence of much serious and widespread "malnutrition."

To my mind the comment of Mr. Udny Yule is just, timely, and proper. No one could be stupid enough to claim that all diets in this country are ideal when it is well known that many are faulty, but I do not believe they are so desperately bad as claimed by some writers. As Mendel said:

> "There is no field of practical importance related to human well-being in which there is greater opportunity for dogmatism and quackery, for pseudo-science and unwarranted prescrip-

* Sir Charles Hastings Lecture (abridged) given under the auspices of the British Medical Association in the McLellan Galleries, Glasgow, February 23, 1937.