niece Agnes a certain tendency to *laesa majestas*—it was only by the gentlest of posthumous rebukes that she and the world were to discover it. Her sister Margaret, he said, was to have the better of the two beds that he had bequeathed them."

Linacre was buried in old St. Paul's before the rood screen of the west door, a spot chosen by himself. His grave was marked by no memorial for more than 30 years, when John Caius, during his presidency of the College, erected a monument to his memory at his own cost. This perished when the cathedral was destroyed in the Great Fire of 1666.

Caius and Gilbert

John Caius, whose presidency extended with intervals from 1555 to 1571, set out for Italy in 1539 and studied physics at Padua under Montanus, the greatest medical teacher of the time. Caius lodged in the same house as Vesalius, the celebrated anatomist, who possibly may have fired Caius's enthusiasm in this direction, for in 1564 Caius introduced anatomies, as they were called—that is, demonstrations of dissections—into Cambridge. These demonstrations were not the first to be held in England, as they had been introduced 20 years earlier at the Barber-Surgeons' Hall in London, where Caius had lectured on anatomy. He is usually regarded as the founder of the study of anatomy in this country. He is said to have modelled his life upon the example of Linacre, and, like him, devoted much time to the collation and translation of Greek medical writers, but, unlike Linacre, he recorded the results of his own observations. These appeared in 1552 under the title of "A Booke of Counseil against the Disease commonly called the Sweate or Sweating Sickness." This is said to be the first instance of a medical book being published in English, but he afterwards republished it in Latin.

It was Caius who designed the insignia by which the President of the College should be fittingly honoured—the cushion of crimson velvet, edged with gold, placed before the President on all solemn meetings, and the caduceus, its head adorned with the arms of the College supported by four serpents, which the President carries to remind him by its material—silver—as Caius quaintly says, to govern with patience and courtesy, and by its symbols, the serpents, with judgment and wisdom. Caius is said to have foretold the very day of his own death, and to have chosen his own epitaph, *Fui Caius*, still to be seen in the Chapel of Caius College.

Dr. William Gilbert, physician to Queen Elizabeth and James I, and President of the College in 1660, published in that year a remarkable book, *De Magnete*, in which he records his experiments relative to the magnet. Gilbert may therefore be said to have introduced the method of experiment into scientific research. By his will he gave his whole library, globes, mathematical instruments, and a cabinet of minerals to the College, but with the exception of a few folios, which cannot now be identified with certainty, these seem to have perished when the College was burnt down in the Fire of London.

I am indebted to Canon F. J. Shirley, Head Master of the King's School, Canterbury, for copies of the wills of Robert Harvey and of John Harvey—both of Folkestone, William Harvey's birthplace—which I gratefully append.

"Archdeaconry Court of Canterbury. Probate records deposited at KCC Record Office, Maidstone.

"PRC 17, vol. 41 (will register), F. 112.

"23 April, 1570. I Robert Harvye of Towne of folkestone—Jone my wife—my house and stable lying at Estbroke—son Roger Harvye—Jone my wife to be exetrx. Witnesses:

John Redhed, John Browne, John Edwardes.

John Cadman, curate of Folkestone mentioned.

"Proved: 7 March, 1570 (-1).

"PRC 13, vol. 13 (Act book), f. 45.

"23 Feb. (1552-3). Admin. of goods of John Harvie of Folkiston' intestate; admin. to Florence widow, sworn, &c. Bound with her Thos. Baker, Jurate of Folkestone, & Hy. Hogben of same yeoman in £40.

"(It is slightly ambiguous as Baker is called *jurat.*=either sworn or jurate. I think it means he is Jurate of the Town of F.)"

In surveying this progress we become conscious of the various phases through which medical endeavour has passed. Contemporary medical practice and knowledge in Linacre's time was a confused mixture of empiricism, folklore, astrology, and magic. Such vestiges of Greek medicine as remained were often tainted, for they had come through the medium of Arabian and Syriac translations from the original Greek texts, and these in turn had been translated again into Latin and contained many inaccuracies. Hermolaus Barbarus, for instance, is reputed to have restored no fewer than two thousand passages in the works of Pliny. Linacre by his careful and accurate translations from the Greek into Latin was able to bring to the notice of his contemporaries the conclusions of Hippocrates, Aristotle, and Galen, based as they were on the simple yet valid foundation of direct observation. By the very nature of things, and to clear the stage, so to speak, he was obliged to look backwards. Caius advanced a step further. In common with Linacre he was strongly attracted to the writings of Galen, and when in Italy had spent much of his time carefully collating the manuscripts of that author, but to scholarship he added the practice of direct observation. This is seen in his devotion to practical anatomy and in his clinical observations set out in his book on the sweating sickness. Gilbert advanced further still: not content with observation, he introduced the method of experiment into scientific research. As Sir Walter Langdon-Brown has aptly said, "Linacre looked to the past for the Revival of Learning, Caius faced both ways, but Gilbert steadfastly looked forward."

THE LOCALIZATION OF DEEP PAIN

BY

J. B. HARMAN, M.D., F.R.C.P.

Physician to Out-patients, St. Thomas's Hospital

This paper is concerned with the laws that determine where a deep pain is felt or, in other words, with its local sign. It is intended to show that the pain is not felt in any particular structure of the body, such as viscera or body wall, but that it is best regarded as a projection from the brain—to show in effect that the place where a pain is felt is determined as much or more by the anatomy of the cortex as by the structure of the limb or part of the body in which it seems to be. The view has indeed been hinted at from time to time, and has received a more definite statement from Lewis (1942). I believe it to be in harmony with current ideas on perception and to provide an explanation for those vexatious experiments with "novocain" block and phantom limbs.

It will not be necessary to review the many theories of the last fifty years, but since our common beliefs are still coloured by the traces they have left behind them it will be better to clear the ground by stating three propositions that may be regarded as proved. The first is that viscera can in fact be pain-sensitive. As is well known, Lennander (1902) popularized the view that they were insensitive, and this was widely held until Hurst (1911) showed that distension could cause pain in the oesophagus and rectum. Since then many other instances have been described in which

pain originated from a viscus, and it is now generally agreed that viscera may be sensitive provided a suitable stimulus is used.

The second proposition is that pains from viscera and deep structures are essentially the same. The suggestion that visceral pains were different from others rested on certain interpretations that have now lost their force. In any case the distinction became meaningless when it was shown (Lewis, 1938; Lewis and Kellgren, 1939) that phenomena which were supposed to be characteristic of visceral pain—such as dull quality, tendency to spread segmentally, associated muscular rigidity, and so on—could be produced equally well by injuring deep somatic structures. Lewis (1942) concluded that the proper distinction is between pains that come from deep structures, like viscera and ligaments, and those that come from the superficial parts, such as skin.

The third proposition is that there is only one kind of deep pain and that it is not divisible into local and referred. These two kinds were postulated to account for the fact that, whereas it could be said that stomach pains coincided with the stomach, it was obvious that angina and renal colic were felt a long way from their site of origin. Again, it was Lewis (1942) who argued that the distinction was unnecessary, for he believed that deep pain always had a spreading segmental distribution. The apparent anomaly is merely due to the anatomical accident that the heart is part of a segment that stretches down the arm, whereas the stomach and the rest of its segment are in roughly the same position.

Pain "In" and "From" a Viscus

The equivocal meaning of language has caused a confusion of thought that must be cleared up before the real problem can be seen. It has, for instance, been tacitly assumed that having a "pain in a viscus" expresses the same notion as having a "pain in a finger." Much experimental ingenuity has been expended on trying to decide whether it is possible to feel a pain in a viscus, yet no conclusions have been or, indeed, can be reached. The problem is not physiological and soluble by experiment, but philosophical and linguistic, and can be settled only by examining the meaning of words. Thus, if a man says he has a pain in his finger, the ordinary English usage is accepted and everyone knows what he means. We all know we have a finger, and we know where it is and we have felt pain in it. But a man could not say with the same meaning, "I have a pain in my Meckel's diverticulum" even if it should indeed be producing colic. For of all those who have suffered this pain there must be few who have ever heard of the organ, fewer still who know they have one, none who could know where it was lying, and all would have felt a pain that was "bigger" than the organ it was supposed to be in. Anyone who makes such a statement is not talking of his perceptions, but is making a diagnosis, assailable by evidence and argument. And he may be proved wrong. But if he said he had a pain in his belly his statement would be accepted, for it is a matter of common experience that men perceive their bellies and that most have had pains in them.

It is therefore important to bear in mind the distinction which is so often overlooked between pains that come from a part and pains that are felt in it. We believe it to be meaningless to say that a man feels a pain in an organ that he cannot perceive, and the implication that an anatomist could feel pains where the layman cannot is absurd. So we must reject any theory of deep pain that admits of its being felt at the site of origin. The problem can then be stated thus: "Where is a deep pain felt that comes from an unperceived structure?" It occurred to me that the

answer might be had from persons with phantom limbs, for they have the perception of a part, yet are unencumbered by its real presence.

Referred Pains in Phantom Limbs

In subjects who had had an arm amputated a deep pain was produced by injecting 6% saline into the interspinous ligaments. The sensations of the normal arm were compared with those of the phantom.

Case 1.—J. J. H., aged 50, had a road accident in 1929 which caused loss of all power and sensation in the right arm. One year later it was amputated at the shoulder. Examined 1940. The phantom remained unchanged all these years. It is immovable and in the position in which his arm was slung before amputation. The arm and forearm appear to be half as long as normal but the hand twice as big. The whole phantom is quite clear. The hand feels as if it is being squeezed, the rest just dull and heavy. The effects of an interspinous injection were:—*Normal arm*: Stabbing and tingling sensation in middle finger and ring-finger when the needle was introduced, becoming more severe with saline. *Phantom*: Tingling in middle finger and ring-finger; the wrist feels as if it is being tightly squeezed, the elbow very slightly so.

Case 2.—F. C. Y., aged 59, had a gunshot wound of the left arm, forearm, and elbow in 1916. Amputation above the elbow was done three months later. Examined 1940. The phantom remained unchanged. It consists of hand and wrist only, placed about 12 in. (30 cm.) higher than normally. The thumb and forefinger are most distinct, the whole part being numb. There is possibly some movement. The effects of an interspinous injection were:—*Normal arm*: Sharp tingling pain in hand and elbow. No aching. "I know something is going on in it." *Phantom*: Similar sensations, but stronger, "like electricity"; distribution is in the inner and outer border of the hand and in the whole forearm, which appeared for the first time; no aching. An injection into the erector spinae muscles was given. It produced severe aching along the inner side of the stump—"rheumatically pain like a bag of nerves"—after a few seconds a numb sensation was felt in the inner and outer border of the phantom hand, different from that in the stump and "more like the return of sensation after a very severe accident."

Case 3.—C. F. M., aged 55, had all the tendons of the right hand cut by a shell splinter during the 1914–18 war. A below-elbow amputation was performed the same night. An immediate phantom was just like a real hand. In 1932 he had a stroke and could not speak for four months. Examined 1940. The right leg and stump were still spastic, the movements of phantom thumb remaining unimpaired. Phantom now smaller than normal and nearer to stump. Injection into erector spinae at base of neck resulted as follows:—*Phantom*: Dull rheumatically pain inside stump at the back of the forearm. Passed into phantom in the back of the knuckles and fingers as a pricking and tingling sensation, quite different from the ache in his stump.

Case 4.—G. M., aged 33, received a gunshot wound at Anzio, with immediate guillotine amputation above the elbow as P.O.W. Clear, complete phantom, still bleeding and itching; he has tried to use it on several occasions. Two months later reamputation was carried out to the shoulder. Examined in 1946. He has three shooting pains at the level of the elbow as if they were in fingers, but no fingers are felt; this appears to be the remains of his first phantom. He also has a dull aching phantom of his first amputation stump. An interspinous injection had the following effect:—*Phantom*: Gripping sensation in the elbow-joint as if something had been tied tightly round it, and there was a cramp. "I often get that feeling if I have a blow on the shoulder—it is very slight." The sensation can be imitated by squeezing the normal arm fairly firmly with the whole hand.

It will be seen that pain does spread down into the phantom, where it sometimes has the normal dull gripping quality of roughly segmental distribution. But at other times it was numb and tingling, and might not be strictly

segmental, being felt only in the elbow or wrist. These are differences from the classical deep pain, but they are not thought to be due to the conditions of the experiment, because such variations may be described by patients with normal angina. Since these experiments were undertaken, Cohen and Jones (1943) have published two remarkable cases with angina pectoris in phantom arms; the arm pain was abolished when the brachial plexus was blocked with procaine. I myself have recently seen another such patient.

Case 5.—A.C., aged 66, had a gunshot wound in 1915 through the upper left arm, which was amputated the next day. The phantom used to be a hand and elbow at a normal distance from the shoulder. The arm has now got shorter and the elbow is represented only by an occasional pain. The hand is clenched and can be opened slightly. It feels "kind of numb and is always warm." Eighteen months ago he became subject to a pain in his chest. It starts in the centre of his sternum, "like a very bad wind pain, turning over and gripping my chest." After a time it works down the arm and is like pins-and-needles in the hand. At first it came on at night in bad attacks once a month or so. It used to wake him up, and he had to stand by his bed. Now it comes on when he walks, always after a certain distance. It goes in a few minutes if he rests. He is a diabetic of ten years' standing. Arteries of limbs and optic disks normal for age. Radioscopy showed the left ventricle slightly enlarged; E.C.G. normal.

These observations prove that it is not necessary for the sufferer to possess the part in which pain is felt. It appears to be sufficient if he feels as though he has it. Now it may be that this phenomenon is merely a sensory perversion of a mutilated body. But it is hardly likely that a phantom bears no relation to normal perception of the body or that it has a special pain mechanism of its own. It will therefore be worth while to consider the hypothesis that deep pains in the intact man are also localized as it were in a phantom that corresponds with his real body. In other words, the solution of deep-pain localization will not be sought in possible changes in the peripheral body where it is felt, or the nerve tracts connected with it, but in the mechanism of body perception, which is a function of the cerebral cortex.

Phantoms and the Body Image

Head and Holmes (1911) used the term "body image" to describe the conception that a person has of his own body—of its size, shape, surface, depth, and movements—by means of which he is able to move parts of the body in relation to the whole, and the whole in relation to the environment. The body image is built up by the higher levels of the sensorium from peripheral sensations. It grows throughout life as these sensations are integrated, and it changes slowly as the real body alters its shape.

In the ordinary course of life the parts of the body are so often found where they are expected to be that it seems that their image and reality necessarily correspond. But there are occasions when they do not. Thus certain hemiplegics may feel as if their arm is stretched above their head, whereas it can be seen lying by their side (van Bogaert, 1934). They have a real arm and a phantom arm separated from it. The amputee loses his real arm, but its image persists. The neuroma continues to transmit impulses that are interpreted, on the basis of previous experience, as "an arm." Parts such as the fingers and joints, of which a person is normally more conscious, tend to persist in the phantom, while the upper arm may be represented merely as a distance that the elbow is from the shoulder. When a phantom goes it disappears piecemeal, the clearer parts remaining till the last, so that in the end it may be nothing more than fingers growing from a stump (Riddoch, 1941). Conversely, cortico-thalamic lesions may cause agnososomia (Nielsen, 1938) in which the image of

the right side of the body is lost but the part remains. The patient does not merely lose sensations from that side; he ceases to perceive it, and if he is shown his arm he cannot conceive that it is his. This amputation of the body image may be so severe that the patient cannot even imagine a right side either to his own body or to the world around him.

If a part is anaesthetized we find a disturbance of the relationship between the body and its image which is peculiar. A patient certainly feels the presence of a blocked arm, for he does not become incapable of conceiving such a thing as he would with agnososomia, nor is he just unaware of it as he is of his pancreas, yet it feels different to him both from a normal arm and from a phantom. An anaesthetized part is usually described as being dead or heavy, so that an arm hangs like an artificial limb from the sentient shoulder and the jaw feels like a swollen prosthesis. In fact, in some respects they cease to feel like parts of the body. This raises the question of how one distinguishes one's body from the environment—an important distinction in this connexion because it is the general experience that pain is felt only in the body and not in surrounding objects. It seems that the boundary is drawn between the body that has, or appears to have, innate sensibility and the environment, which, however much sensation may be projected into it, does not itself "feel." On the one hand we have the trunk, limbs, and phantoms; on the other, hair, clothes, and tools, which are perceived to be distinct, though, as Head and Holmes (1911) remarked, they may be incorporated into the body image. In this latter class we put also real parts of the body, such as colostomies, prolapses, and anaesthetized members, which are equivalent to the environment because they cannot feel, but are carried round with the same care and sense of ownership as a hat or stick.

Deep Pain and the Body Image

In the normal man deep pains are felt inside the body. This is consistent with the body image's property of having depth as well as surface. Although the pains are felt deeply they are confined to regions nearer one surface than another. There is a strong tendency for these regions to be in the front of the body even when the stimulus is near the back, but there is less tendency for a pain arising near the front to be referred backwards; in fact, a pain arising more or less centrally is usually referred to the back only after it has reached a certain intensity in the front. There is also a tendency for trunk pains to be referred down the limbs, and pains within the limbs to be more pronounced in the joints than in the length between. On the other hand, deep pains arising within the limbs spread back beyond their origin only if they are severe. This distribution corresponds with the more vivid parts of the body image, for the individual has a clearer consciousness of the front of his body than the back, of his limbs than his trunk, and, as phantoms show, of the joints than the segments between. An unsophisticated housewife was asked why she thought her angina was worse in her elbow than in her arm. She replied, "I suppose it is because you feel your elbow more, don't you think?"

Organic pains are sometimes distributed in an unusual way, referred to scars, or felt more intensely over significant parts such as the heart or appendix. There are also indications that pain may be diverted from its usual site to some other part that has been rendered habitually painful by another stimulus, such as gall-bladder pains that are referred to the left arm in subjects prone to angina (Jones, 1943). Those who have written much on the subject of deep pain (Head, 1894; Mackenzie, 1918; Lewis, 1942) have been forced, after expounding their views, to point out that there

are always cases of bizarre distribution which cannot be explained. It must indeed have been the experience of most physicians that patients will on occasion persist in describing pain references which do not correspond with any known mechanism. Possibly some of these will be found to depend on unsuspected peripheral lesions. But others may well be determined by some higher cerebral organization, and this may be found in variations of the body image. Such variations exist; for some people, for example, have an accurate conception of their body and are skilful in its use, while others are clumsy and uncontrolled. Further, vividness of parts may be enhanced by past events or peculiarities of temperament—the amputation phantom remains crushed and bleeding as the real part was—and studies of normal and abnormal psychology indicate the differing values that men may give to parts of their bodies. Since the body image itself can vary, some variation in pain reference would be expected.

The interpretation of procaine-block experiments in these terms is that pains are not projected to anaesthetized parts, because they are in effect equivalent to the environment. Pains are always felt in what appears to the sufferer to be his own body, and even if he only knows he has a pain "somewhere" it is never somewhere outside himself. Those, however, who have tried to abolish deep pains by local anaesthesia have had conflicting results (Lemaire, 1926; Weiss and Davis, 1928; Rudolf and Smith, 1930; Morley, 1931; Woollard, Roberts, and Carmichael, 1932). No doubt this is partly due to the difficulty of experimenting with deep pain and to confusing it with reflex hyperaesthesia, but the unjustifiable assumption has usually been in the mind of the experimenter that the pain must be either "in the viscus" or "in the body wall." A straight answer cannot be given to a question that ignores the possibility of its being in neither. The discordant results can, however, be reconciled by the present hypothesis, for how much of a pain can be abolished will depend on how much of it is projected into the interior or surface of the body image, and on how completely these parts can be anaesthetized. It is, for example, relatively easy to abolish an anginal pain that is deep in the arm by blocking the brachial plexus. The pain that is felt near the surface of the chest can be banished or modified by anaesthetizing these parts. It may reappear in a neighbouring area, to be chased to yet another when that is blocked in its turn (Jones, 1943). This is an artificial alloaesthesia in which pain is diverted to the new site, or is noticed for the first time in it, after the most favoured part of the body image has been destroyed by anaesthesia. On the other hand, the pain that is felt deep in the chest always remains in these experiments, however many anaesthetic patches are produced on the surface. This has been interpreted as the true local pain felt in the viscus. But it is better regarded as pain persisting in the interior of the body image. The internal pain remains because the spatial perception of the chest into which it is projected is unaffected by such procaine block as is practicable. Indeed, perception of the anterior could not be abolished without anaesthetizing so much that the visceral afferents themselves would be interrupted at the same time.

The argument that deep pain spreads because it cannot be localized to the unknown region where it arises needs some elaboration, for there are parts of the body that are very accurately perceived yet give deep pain. For example, the finger-joints are particularly vivid in the body image, and we are certainly aware of the position and movement of muscle masses or imbedded bones, but all of them give poorly localized deep pain. In other words, why does not pain from these parts have a local sign that approaches the accuracy of that in the skin? This question cannot of course be properly answered without understanding the

mechanism of local sign in the skin itself, but it may be observed that there are various modes of perception which are not all equally important in giving local sign. Sensations such as touch are concerned with the body surface only, of which they give a very detailed map; while proprioceptive sensations are the basis of perception of body space, position, and movement. Perception of a finger-joint is a combination of both, built up from perception of its surface and knowledge of the space it encloses. But our knowledge of this space is limited to its shape and dimensions, and the map of the interior is as blank as that of the trunk. Stimuli in both are in *terra incognita*, and the pain that results has the same characteristics. Inevitably a deep pain in a finger must, if it is to remain in the body, be confined to a smaller space than a pain in the abdomen, and for this reason will give the impression of being more accurately localized. But this is a false impression, as can be seen by considering angina. The pain that spreads to the finger seems to be more accurately placed in the body than the pain in the chest, but this is not an accuracy of local sign, for the pain is felt a whole arm's length from where it arose.

Deep Pain and the Segment

In discussing the body image we have been exclusively concerned with the higher analysis of deep pain. But the region in which pain is felt must be determined to a large extent by the fixed structure of the nervous system, for otherwise all pains from unperceived organs would be felt together in the most vivid part of the body image—in the face or hand, for example. It has been recognized for fifty years (Ross, 1888) that this region was the spinal segment, and we have to inquire how it is that the sensation of pain caused by a cardiac infarct, for example, becomes segmental and spreads to the arm. This radiation was originally supposed to occur in the cord, because this is where the sensory nerves from the whole segment are first grouped together. Although there is some interconnexion here, as reflex rigidity and hyperaesthesia show, it is difficult to imagine any possible mechanism at this level, and certainly none has been demonstrated (Lewis, 1942). Even in the last century (Sherrington, 1898) it was shown that local sign of superficial sensations must be a function of the brain, for it certainly was not an inherent quality of any sensory nerve. Thus burning a finger sets up impulses characteristic of pain alone, and not of "pain from a finger." The assigning of a place to the crude sensation depends on the integration of other sensory impulses and on the fixed structure of the sensorium where it occurs. If the same holds good for deep pain one would expect to find some evidence of segmental anatomy in the cortex to account for this type of spread. Such is the case, for recent work with fine methods of cortical analysis proves that "the body surface is projected dermatome by dermatome upon the post-central gyrus. The serial order is that of the dorsal nerve roots except that the cervical segments appear in the reverse order" (Fulton, 1943). Most of the work has been done on primates and has been concerned with superficial sensation and movement, but there is every reason to believe that the general style of cortical architecture is the same in man, and that it applies to deep pain also. The segmental spread of deep pain may then be regarded as nothing but a sign of activity at a certain level of the nervous system. We can say what that level is from the symptoms, just as we can diagnose the site of a lesion from the type of palsy or fit it produces. The segmental disturbance does not occur at the highest sensory level, for the segment does not exist in the body image—no man perceives his segments in the way that he is aware of his hand or mouth. So perhaps it is not surprising that pains are rarely

left filling such a meaningless territory as this, but are modified in the way that has been noted until they correspond with the body as the sufferer perceives it.

Summary

Deep pain, unlike superficial sensation, comes from parts of the body that are unperceived and to which, it is argued, no sensation can be localized. All sensations are normally felt somewhere, and deep pain must therefore be an alloaesthesia. It is suggested that these "pains from nowhere" are projected into the perceived parts of the body. They have a segmental basis derived from the fixed structures of the cortex. Their locality is further defined within these crude limits according to the individual characteristics of the body image. The sensation of deep pain does not depend on any peripheral change in the part where it is felt. But its location does depend on the normal stimuli coming from the part, for without these the place would remain unperceived.

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THE PRE-ERYTHROCYTIC STAGE OF MAMMALIAN MALARIA

BY

H. E. SHORTT, M.D., D.Sc., D.T.M.&H.

Director, Department of Parasitology, London School of Hygiene and Tropical Medicine

P. C. C. GARNHAM, M.D., D.P.H.

Reader in Medical Parasitology, University of London

AND

B. MALAMOS, M.D., D.T.M.

Lecturer, University of Athens

Since the discovery of the part played by the mosquito in the transmission of malaria there has remained a gap in our knowledge of the cycle of events. This has been our complete ignorance of what happens to the sporozoites injected by the mosquito during the period between its bite and the appearance of erythrocytic parasites in the circulating blood. Schaudinn's (1902) observation of the sporozoite entering a red cell has never been repeated and has long been suspect, and the most generally held theory of recent years has been that some form of development takes place in the internal organs—probably in the reticulo-endothelial system—before the parasites enter the red cells of the circulation at the end of the incubation period. This interval may be considered to be a period of about ten days.

The curtain was first really lifted in the case of avian malaria when James and Tate (1937) described the exo-erythrocytic cycle in *Plasmodium gallinaceum*, but the developments following the introduction of sporozoites by the mosquito remained a mystery.⁶ The next step was the discovery by Mudrow (1940) and Shortt, Menon, and Iyer (1940) of developmental forms of *P. gallinaceum* in the incubation period; these were schizogony forms in reticulo-endothelial cells. Reichenow and Mudrow (1943) next gave a detailed description of the forms found during the incubation period in infections with *P. relictum*, and Huff and Coulston (1944) independently described in even greater detail the course of events in *P. gallinaceum*.

All this work led to the belief that some parallel development must take place in the case of mammalian (including human) malaria, but all attempts to demonstrate this proved unsuccessful. Efforts to discover the incubation period stage of mammalian malaria—i.e., the hypothetical pre-erythrocytic stage—were given a stimulus by the work of Fairley (1945) at Cairns, Australia, during the recent world war. Fairley and his co-workers showed that during the biting act of the malaria-infected mosquito, and for about half an hour afterwards, blood inoculated from the bitten person into a volunteer produced an infection. After this period and until the appearance of the parasites in the circulating blood even large quantities of blood from the volunteer produced no infection in another individual.

From these results and others obtained in the field of chemotherapy—for example, Davey (1946)—it was evident that shortly after the introduction of sporozoites they disappear from the circulation and the further development during the incubation period takes place in some protected site outside the general circulation.

Hitherto there has been little to support this hypothesis in the form of actual findings in mammalian malaria. Raffaele (1937) described bodies found in smears of human bone marrow and considered by him to represent stages in the development of sporozoites. Somewhat similar observations have been made by other workers in this field up to the present date, but none of these have been confirmed or have even received much support.

Large-scale experiments with *P. cynomolgi* carried out by the Mammalian Malaria Inquiry under the Director, Central Research Institute, Kasauli (1946), and similar investigations by Huff and Coulston (1947), have yielded negative results.

In the Department of Parasitology at the London School of Hygiene and Tropical Medicine investigations to discover the pre-erythrocytic stage of *P. cynomolgi* in the rhesus monkey have been in progress since 1945, and the most recent experiments have at last resulted in the discovery of this stage, as briefly reported by Shortt and Garnham (1948).

Description of Experiment

We do not propose to give the details of all our work, but will confine ourselves to a description of our most recent successful experiment. More than 1,000 *Anopheles maculipennis atroparvus* bred in the laboratory were fed on a monkey showing mature gametocytes in the peripheral blood. The mosquitoes were subsequently fed on another infected monkey and were given a third feed on the original animal. The interval between the first and third feeds was eleven days. The mosquitoes were maintained at 26° C. in a relative humidity of approximately 80%.

Ten days after the last infective feed 20 mosquitoes were dissected and without exception proved infected, most of them with extremely numerous sporozoites in the glands.