THE TEETH AS A SOURCE OF FOCAL SEPSIS.

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Definition.

A focus of infection is a chronic lesion where septic organisms have secured a foothold in a necrotic nidus from which soluble toxic matter may diffuse into the adjacent living tissues and be carried thence all over the body. From such a focus these same organisms may sometimes be dislodged by relatively slight traumatic interference and propelled into the bloodstream.

The term "focal infection" is applied to that condition of general ill health which arises as a result of the presence in the body over a long period of such a focus. Examples of these foci are the infected root canals of a tooth or the crypt of a tonsil. There is obviously a significant difference between the dissemination of the organisms themselves and the diffusion of their toxic products.

Pathology.

The organisms concerned in oral infection are principally the streptococci and the group known as viridans is invariably present. The local lesions can, however, all be produced experimentally with any of the septic organisms; and though in the mouth, contaminating organisms enter and complicate the experiment, it is possible to produce quite comparable bone lesions with pure cultures elsewhere in the body, where contamination can be prevented. In this way it can be shown that the local lesions are not specific reactions due to the introduction of one particular organism, but are simply examples of the ordinary reaction of the tissues to septic invasion; and indeed it is equally true that the lesion cannot be produced by merely introducing organisms, whatever they be, into the oral cavity. An animal will lick the pus from a suppurating wound but that will not cause pyorrhœa. The development of a lesion depends entirely on the local terrain and the mode of implantation of the organism. Any of the pus producing organisms will produce the lesion if these are conducive and the infection rapidly becomes a mixed one.

The chronicity of the lesion depends on the opportunity offered to the germs to maintain a footing in contact with the tissues, but protected from attack by the polymorphonuclear leucocytes. It is the unique opportunity afforded by the dental tissues for such a footing which makes them a constant source of focal infection.

The classical instance is the "dead tooth." An acute abscess occurs in the pulp and the pulp is either removed or allowed to die. In either case the apical canals of the root may become infected and the organisms continue to grow there in the serum which diffuses in from the periapical tissues. It makes little difference whether the main pulp chamber is filled or not, the organisms in the minute canals get all they need from the serum and their toxic products diffuse out into the tissues in exchange. They themselves cannot, however, grow out into the periapical tissues because polymorphonuclear leucocytes guard the entrance. Conversely the leucocytes cannot crawl into the minute canals and exterminate the organisms. This state of stale-mate is the essential local factor in focal infection.

In order to obtain an accurate picture of the significance of such a focus in the community of cells which forms the body it is useful to consider the results of a deliberate implantation of one of these organisms into bone. A pledget of cotton wool, dipped in a broth culture of a staphylococcus, or of streptococcus viridans or

even of streptococcus hæmolyticus is introduced into a small hole which has been drilled into a convenient bone, such as the iliac crest or symphysis menti of an experimental animal. The wound is closed loosely with a suture and in forty-eight hours is suppurating freely. After seven days the animal is killed and the bone sectioned serially. The serial sections are stained alternately with hæmatoxylin and eosin, then Van Gieson stain for the collagen, and Gram stain for the organisms. Fig. 1 (Art Plate) shows a strip of the section running from the centre of the lesion at one end to the periphery at the other.

Careful examination of these sections indicates that the lesion may always be divided into four perfectly definite zones. Comparison of the gram sections with their neighbours shows that of the four zones only the central one contains the actual organisms, and also that it alone contains the polymorphonuclear leucocytes. The organisms are confined to this central **"Zone of Infection"** and are prevented from growing beyond it by the leucocytes. The presence of any appreciable collection of leucocytes therefore means the actual presence of the organisms themselves, and *vice versa*.

The reaction in the other three zones must correspondingly be due to the presence of soluble toxic matter diffusing into the tissues, and the presence of the poison is indicated by the enormous number of round cells which are attracted to the part. In the zone nearest to the centre the concentration of this toxic matter is so intense that every normal cell is dead; the bone corpuscles have disintegrated and their lacunæ are empty. The fibroblasts have disappeared and the intercellular collagen network of the loose connective tissues contains only round cells and histiocytes. This is the **"Zone of Contamination."**

Towards the periphery of this zone the toxic matter is naturally more dilute and a point is reached where the osteocytes are seen to survive so that the lacunæ of the bone still contain their normal occupants. *At precisely this level osteoclasts make their first appearance.* The osteoclast is perhaps the most interesting and in many ways the most important cell in chronic irritation of bone. It certainly is so clinically, since it is responsible for the destruction of the bone matrix which disorganises a joint, sets free a sequestrum or loosens the teeth, and the result of its activity paints the X-ray picture. It is therefore of the utmost importance in radiological interpretation to know the conditions under which this cell can live.

These conditions are extremely specialised and clearly defined, so that if it is possible to say that bone is being actively absorbed at a certain point the degree of toxic irritation can be accurately assessed.

For instance osteoclasts are not able to live in an environment which is so contaminated that it kills the bone corpuscles, much less of course in the presence of actual infection. On the other hand they do not appear further away from the lesion where the toxic matter reaches its final effective dilution. They are a response of the undifferentiated mesenchyme to a precise degree of irritation; either less or more will fail to produce them or if they are present will cause them to disappear. We may therefore define this zone as **"The Zone of Irritation."**

The fourth zone commences quite abruptly at a point immediately beyond the last osteoclast. There is no overlap but quite suddenly instead of bone destruction new bone or callus is being formed at almost incredible speeds by osteoblasts. It appears that the moment a certain point in the concentration of the toxic matter is passed the undifferentiated mesenchyme cells grow into osteoblasts rather than

osteoclasts and *pari passu* young fibroblasts are seen weaving a new network of collagen fibres. Here there are very few round cells to be seen and this zone is "The Zone of Stimulation."

It has been described elsewhere (Fish, 1939) how this ordered activity results in sequestration and the filling up of the gap in the bone and how at each stage the rules are obeyed. They may be formulated for our present purpose:—

1. The presence of the organisms is always associated with a massive infiltration of polymorphonuclear leucocytes.
2. The presence of soluble toxic matter is always associated with the presence of round cells.
3. The response of the undifferentiated mesenchyme cells of bone to strong toxic irritation in the production of osteoclasts.
4. The response to weaker stimulation is the production of osteoblasts.

It is quite natural that polymorphonuclear leucocytes should go right up to the organisms and surround them for they are phagocytes and live on solid food. Normally this consists of the debris of the red blood corpuscles, but Fig. 2 (Art Plate) shows not only how the organisms grow into inaccessible crevices and so establish themselves but how diligently the leucocytes pursue them. The round cells on the other hand never go right up to an organism. They have not got enough cytoplasm to engulf one and so they live on soluble food. They would therefore be taking an unnecessary risk if they were to go too far, but that they are particularly attracted by soluble toxic matter is shown not only by the heavy infiltration which always surrounds the polymorphonuclear barrier but by their choice of habitat in the lymph nodes.

Now it is clearly important, in such a disease as chronic arthritis for instance, to know whether it be the organisms themselves or their toxic products which are producing the reaction in the tissues at any given point in the body. It is equally of value to know that the degree of bone absorption varies with the degree of tissue irritation.

It is therefore fortunate that we have this simple histological and radiological test by which we can define the distribution of septic organisms in the tissues. So far as staphylococci and streptococci are concerned if a concentration of polymorphonuclear leucocytes is observed we may be sure that there are actual organisms at the centre of it. If the tissues are merely infiltrated with round cells there is only soluble toxic matter present.

This is of the greatest value in dental pathology for it is seen that in the case of an infected dead tooth, for instance, the organisms are confined to the debris in the root-canal by a small cordon of leucocytes which at once engulf any organism which grows out and which may even squeeze into the canal in search of them. Beyond this cordon there is an intense infiltration of round cells which extends all round the apex in the periapical tissues—the so called apical granuloma—which indicates that a very considerable amount of soluble toxic matter is diffusing out into the tissues. This is the zone of contamination in which no normal cell survives; beyond it is the zone of irritation where the bone absorption has produced the "apical rarefaction" of the dental skiagram.

Similarly, the ulcerated epithelium lining a pyorrhœa pocket shows at the surface of the ulcer a layer of polymorphonuclear leucocytes, many of which have even crawled out into the debris. Below the surface is seen an even more extensive infiltration of round cells than appears round an infected apex, because more toxic

matter is soaking in. Beyond this again is the absorption of the tips of the alveolar crest and often "sclerosis" of bone round the tooth apex.

There has been so much misconception about the presence of organisms "of low virulence" amongst the living tissue cells that more substantial evidence than mere histological interpretation is needed to demonstrate that it is impossible to have organisms wandering about in the tissues unheeded by the predatory leucocytes. Fortunately such evidence is available and the fact may be demonstrated quite conclusively in another way.

It is common experience that when a tooth, even a living tooth, is extracted and cultured it is almost always possible to grow a streptococcus from the apex, or indeed from the pulp, and thus it has been assumed that organisms have their normal habitat in the periapical tissues.

The fallacy of this extraordinary conception may easily be demonstrated by cauterising the periodontal sulcus where the organisms really live with the actual cautery before extraction. In this way the sulcus is sterilized and the apex will then be found invariably to be sterile too provided great care be exercised in the extraction to avoid chance contamination, and of course provided the tooth is alive (Fish and Maclean 1936). The apex will still be sterile however much pyorrhoea there may be from the pocket provided only that the cautery wire is carried to the bottom of the pocket all round the tooth. It is not of course sufficient to wipe out the pocket with iodine and indeed the trauma of attempting to do so may well drive the organisms into the blood vessels of the parodontal membrane, whence, after extraction, they may be cultured.

In this singularly dramatic instance, therefore, where if ever, organisms might be expected to reside either amongst the round cells, the absorbing bone or the broken down fibres of the tooth attachment, it has nevertheless been conclusively shown that the tissues are sterile.

We are therefore led to the conclusion that the experimental findings are right and the tissue changes are in fact due to a soluble irritant. The local lesion may thus be described as a constant source of toxic absorption. Nevertheless there are circumstances under which the actual entry of organisms into the body from such a focus may occur. Trauma to the lesion may momentarily disturb the protective barrier of leucocytes and send showers of bacteria into the blood stream.

Okell and Elliott (1935) recovered mouth organisms from the median basilic vein a few minutes after extraction of a tooth. Round, Kirkpatrick and Hails (1936) recovered them in the same way a few minutes after patients suffering from pyorrhoea had been allowed to chew hard sweets, and we ourselves (1936) were able to show the organisms histologically, caught in transit as it were at the moment of extraction, in the vessels of the pulp of an extracted molar.

The organisms thus get into the blood stream from the parodontal sulcus with great facility when there is ulceration present. Even the slight trauma of chewing hard food may cause the small marginal ulcers to bleed and the rocking to and fro of the teeth during subsequent mastication pumps the organisms into the blood vessels of the parodontal membrane which run from the gum margin past the apex of the root. It is this occurrence during extraction which causes the apices of most extracted teeth to be reported upon as "infected."

The freedom with which a bacterial shower into the blood stream may occur, appears to stand in marked relationship to the elaborate precautions which nature

has taken to prevent the permanent lodgment of an organism in the tissues, and in fact the fate of these microbes which enter the blood stream is even more rapidly sealed than if they had been pushed into the fixed tissues. The leucocytes or the reticulo-endothelial cells devour them with just the same celerity and within a few minutes or hours at most the blood is once more sterile.

Before discussing the effect of either the toxic absorption or the bacteriæmia on the system generally, some reference may be made to the clinical signs of the local lesions.

Clinical signs of the local lesions.

Apical infection occasionally causes a sinus if there has been an acute onset but more often there is no external sign. *It can only occur on a dead tooth* and it may be possible to suspect that a tooth is dead from its colour and the position and size of the filling; if the tooth be carious and unfilled it may be possible to demonstrate an empty root-canal.

Radiographic evidence is however most important though even that is not always conclusive. The root-filling may show, radio-opaque, all down the root-canal or perhaps at least at its entrance. If there is any toxic matter escaping from the root-canal into the surrounding periapical tissues the bone will show some sign of absorption and this is generally radiographically visible though it may be obscured by the shadow of the root itself. If there is no break in the lamina dura of the socket round the apex, it is unlikely that any toxic matter is escaping into the tissues.

In obscure cases only a dental surgeon can give a final verdict as to whether a tooth is alive and then perhaps only after an exploratory incision into the dentine.

Marginal infection. This condition is associated with ulceration in the parodontal sulcus. The gum margins are often hyperæmic and dark red in colour but the tendency to bleed when interfered with is the most important sign. The ulcers are actually inside the parodontal sulcus and so are not visible but they will bleed readily if the pocket be explored with a blunt probe. In this pocket pus and debris are found and indicate the degree of activity of the lesion. The depth of the pocket indicates the extent to which the fibrous attachment of the tooth has been destroyed by the poison and the looseness of the tooth is an indication of the degree of bone absorption.

The radiographic picture shows bone absorption at the tips of the interdental septa which have a feathery edge instead of a lamina dura. There is often "sclerosis" or bone deposition deeper down in the region of the root apices where the toxic matter is more dilute. The degree of bone absorption is an indication of the extent to which the connective tissue is susceptible to the amount of soluble toxic matter which is reaching it. The greater the concentration of this poison and the more susceptible the tissues the greater will be the amount of bone absorption. It will be realised very graphically in this way how much more toxic matter is absorbed into the body from marginal infection of the gums than from an apical granuloma and it is of course exactly the same material.

The thickness of the periodontal membrane in a skiagram is generally an indication of mechanical stress; and the looseness of a tooth upon which undue biting strain has been placed, owing to the extraction of other teeth, must not be mistaken for the results of infection. Both are due to irritation, in one case mechanical, in the other toxic; in both cases bone is absorbed but in the former there will not necessarily be any marginal ulceration. Relief of this undue strain, the so called "traumatic occlusion," by grinding will permit such a tooth to tighten

FIG. 1.—Photomicrograph (X67) of a H&E section of mandible of guinea-pig, 7 days after experimental implantation of Staphylococci at (F). F, F.I = zone of infection; polymorphonuclear leucocytes and organisms (see Figure 2). C, C.I = zone of contamination; empty bone lacunæ and all normal cells destroyed. Round cells and histiocytes only present. R = zone of irritation; bone corpuscles survive and osteoclasts (O.C.) appear. A fibrous barrier (B) separates this zone from the Zone of Stimulation (S) where the new bone or calcific repair tissue is growing.

FIG. 2.—Higher magnification (X 950) of F Figure 1. Polymorphonuclear leucocytes are seen squeezing into the almost inaccessible crevices where the organisms still flourish. Most of the organisms not so protected are already engulfed in the cytoplasm of other leucocytes outside.

up but will not cure marginal ulceration if any be present. Conversely of course, grinding the occlusal surface will be useless in a tooth which has loosened on account of bone absorption associated with ulceration and not on account of mechanical stress.

It is now possible to summarise this description of the local foci of infection from the aspect of its *influence on the general health*.

1. The organisms are confined under normal circumstances to necrotic crevices where they live and multiply on the serum which diffuses into them.
2. Toxic matter constantly diffuses out into the surrounding tissues and may be carried thence all over the body.
3. Periodically local trauma although even slight may dislodge the organisms and set them free into the blood stream causing a transient bacteriæmia.

General effects.

We may, therefore, consider what becomes of the soluble toxic matter which diffuses into the body from such a focus and also what may be the result of bacterial showers into the blood stream.

The experimental work referred to leaves no doubt that the result of contaminating the matrix of bone or the intercellular collagenous fibres of loose connective tissue is to bring about grave modifications in their structure. The normal cells die and the matrix is destroyed by osteoclasts or histiocytes which are apparently produced by the undifferentiated mesenchyme cells in response to the same toxic influence. If the degree of irritation is less, then the matrix is not eaten away but the osteoblasts and fibroblasts are stimulated so that they lay down additional quantities of matrix or of collagenous strands, that is sclerosis or fibrosis.

This reaction is far less specific than might be supposed. For instance if thymol be introduced into the bone in the same way as the culture of staphylococci a completely comparable response will be seen, and indeed it would appear that these changes are a typical mesenchyme response to irritation.

It is very significant that not only are most of the cells concerned in these local reactions of mesenchyme origin, but most types of mesenchyme tissue are represented, the bone cells—osteoblasts, osteoclasts and bone corpuscles—fibroblasts, blood cells, histiocytes, and the endothelium of blood vessels are all present. Indeed cartilage and smooth muscle are the only missing members of the group. It is, moreover perhaps not a pure coincidence that this group of tissues is the one most concerned in the various forms of chronic arthritis and fibrositis and also that the toxic matter which enters at the site of a focus of infection does circulate to some extent and so reaches these tissues.

This poison, of course, is largely taken up locally by the round cells which are attracted to the part by it, and some of it no doubt is carried down the lymphatics and will be destroyed in the lymph nodes by other lymphocytes. The rest, however, gets into the blood stream and may reach any of the cells in the body before it is ultimately destroyed by the liver and kidney.

It is possible in a patient whose mesenchyme tissue is sensitive to this poison that changes will take place either in the joints or at points of maximal static stress around them where tissue fluid may stagnate, and these changes will be of a nature similar to those found at the site of infection. Bone is absorbed or deposited, and ligaments swell. Round celled infiltration, fibrous replacement, histiocytes, osteoblasts and osteoclasts all enter into the picture. The cartilage change is the only new feature and that again is mesenchyme.

There are other morbid conditions in which focal infection has been regarded as an ætiological factor. Fibrositis whether of the sheath of the sciatic nerve or of the fasciæ of the lumbar muscles is one, and is also an affection of connective tissue.

Endarteritis and atheroma occur in mesenchyme tissues and here in the medial sclerosis of Mönckeberg the last member of the mesenchyme derivatives—the smooth muscle, is seen to be affected and may even calcify.

If then it be true that the tissues of mesenchyme origin are particularly susceptible to exogenous toxic substances the wide distribution of the tissue might well account for the multiplicity of diseases which have been attributed to focal infection. Nor is it surprising that the connective tissue should be sensitive in this way since the scavenger functions of the body are carried out primarily by this type of tissue.

The coincidence may of course be entirely due to the fact that these tissues not only form, but are also responsible for the repair of the supporting structure of the body whatever may be the source of the injury. Moreover they are also concerned with the removal of waste products not of external origin. Trauma and even metabolic waste products could therefore confuse the issue as they frequently appear to do.

There is a different reason for certain specific results of the toxic absorption associated with focal infection. The liver is directly concerned with the excretion of these poisons and as shown by Sir William Willcox (1921) they may produce toxic jaundice. The kidney may similarly be affected. Finally there is a strong body of clinical evidence that pus swallowed constantly may induce gastritis and give rise to morbid conditions in the alimentary canal.

It remains to refer to the dangers of bacterial showers from the ulcers at the gum margins. The organisms would of course normally be killed by the leucocytes in a few minutes or at least collected into the reticulo-endothelial tissue of the spleen where they would be eliminated. There are however a few possibilities of serious consequences which are serious enough to make the indiscriminate extraction of infected teeth occasionally fatal.

In simple endocarditis when there are fibrinous vegetations on the heart valve a bacteriæmia might implant an organism and precipitate a fatal infective endocarditis. Patients in this condition, and especially children should not only be protected from any dental extraction but chewing hard food or the use of a tooth brush is dangerous if there is marked marginal gingivitis. In such cases a paste of zinc oxide and oil of cloves into which strands of cotton wool have been incorporated should be packed round the teeth (Fish 1938) very gently and left for a few days. This should be repeated until the local and general conditions subside. If a tooth must be extracted the sulcus should be cauterised before the operation.

It has been suggested that a leucocyte may ingest an organism in a case of bacteriæmia then migrate into the tissues and finally die there before the organism itself had been killed. If such a thing did happen the dead leucocyte and the organism would no doubt both be rapidly eliminated by other leucocytes and histiocytes, for if the organism proved attractive to the first polymorphonuclear leucocyte it might well prove attractive to another. Of course if it were not destroyed a localised abscess would form, for it could not live unmolested in the tissues. Such an occurrence might then account for a rare case of acute osteomyelitis but it could have no bearing on chronic rheumatism in which abscess formation never occurs.

Even in osteomyelitis the more probable explanation is that a slight blow on the bone occludes a vessel in which organisms happen to be circulating from a recent bacterial shower and the organisms thus trapped in the thrombus have a reasonable opportunity of growing and starting the disease. Considerable strength is given to the latter hypothesis since it is generally small boys with dirty teeth, and bones exposed to trauma which exhibit osteomyelitis. If an organism were similarly trapped in a thrombus in a bruise of the soft tissues it would be so readily accessible to leucocytes from all round that it would not get the same opportunity for unmolested multiplication as it does in bone.

Treatment.

This is both local and general.

Local treatment is purely dental. Apical infection is eliminated by extraction of posterior teeth and apicectomy of anterior teeth. Marginal infection is treated by gingivectomy to eliminate the gum pockets and render the actual epithelial attachment of the tooth accessible. This must be followed by constant daily friction to harden and keratinise the surface of the gum margin so that toxic matter may no longer diffuse in or organisms get pushed into the blood stream (Fish, 1935).

General treatment. This is also outside the scope of the present paper for another and obvious reason. So far as vaccine therapy is concerned it may however be observed that it is not very useful to try to produce immunity to the organisms because they are not in the tissues in a biological sense. Such immunity might minimise the dangers from bacterial showers but would not affect the amount of damage done by the toxic matter circulating in the blood stream. It was natural that much should have been expected of this form of therapy when it was thought that the organisms were actually living in the tissues as, for instance, in the joints in arthritis. It would now appear that some sort of antidote to the soluble toxic breakdown products of these lesions would be of more value.

Summary.

1. A focus of infection is a localised chronic septic lesion from which toxic matter constantly diffuses into the surrounding tissues and whence septic organisms may be dislodged by slight trauma so that they enter the blood stream as a bacterial shower.

2. In order to survive in the body as a chronic infection septic organisms, whether of low virulence or not, must find a necrotic crevice such as the root-canal of a dead tooth, a bony sequestrum or a pyorrhœa pocket. The tissues surrounding such a necrotic nidus though infiltrated by round cells are always sterile.

3. An appreciation of the full significance of this fact is of fundamental importance in studying focal infection. The histo-pathology of the tissues is therefore described and reference is made to the experimental evidence.

4. The clinical and radiological diagnosis and assessment of the local mouth lesions are discussed shortly.

5. The effect of soluble toxic matter on the local connective tissue and its remote effects on similar tissues of mesenchyme origin in the joints and elsewhere are compared. Possible dangers of a bacterial shower are described.

REFERENCES.

- FISH, E. W. (1939), *Journ. Amer. Dent. Assoc.*, **26**, 691.
FISH, E. W. and MACLEAN, I. H. (1936), *Brit. Dent. Journ.*, **61**, 336.
OKELL, C. C. and ELLIOTT, S. D. (1935), *Lancet*, **2**, 869.
ROUND, H., KIRKPATRICK, H. J. R. and HAILS, C. G. (1936), *Proc. Roy. Soc. Med.*, **29**, 1552.
FISH, E. W. (1938), *Lancet*, **2**, 558.
FISH, E. W. (1935), *Brit. Dent. Journ.*, **58**, 531.
WILLCOX, W. H. (1921) *Brit. Med. Journ.*, **1**, 804.