Number of Towns Showing Given Infant Mortality Rate in 1945-6 and Given Poliomyelitis Incidence in 1947

Poliomyelitis Attack Rate per 100,000 Inhabitants	Infant Mortality Rate per 1,000 Live Births					
	Under 30	30-39	40-49	50-59	60+	Total
Under 5	—	18	12	10	4	44
5-9	1	23	19	12	8	63
10-14	2	18	23	11	6	60
15-19	7	18	8	11	2	46
20-24	2	7	6	4	—	19
25-29	1	2	2	7	1	13
30+	3	11	5	6	3	28
Total	16	97	75	61	24	273

Percentage Distribution					
Under 10	6.3	42.2	41.3	36.1	50.0
10-19	56.3	37.1	41.3	36.1	33.3
20-29	18.8	9.3	10.7	18.0	4.2
30+	18.8	11.3	6.7	9.8	12.5
Total	100.2	99.9	100.0	100.0	100.0

over 60, it might be thought that there was at the lower end a slight excess of towns with a high poliomyelitis incidence and at the upper an excess with a low attack rate. But the numbers of towns in these extreme categories are small and the scatter of poliomyelitis rates obviously very wide. Clearly, therefore, a very favourable rate of infant mortality, and thereby, as a rule, favourable social conditions, need lead to no alarm that an unduly high incidence of poliomyelitis will inevitably, or even probably, be experienced in an epidemic year.

Experience of London

The incidence of poliomyelitis in London in the 1947 epidemic has been studied in detail by Daley and Benjamin (1948). To test the relationship between incidence and social conditions they correlated the attack rate in the 28 boroughs with the proportion of males aged 14+ who were in social groups IV and V at the 1931 census (the least skilled occupationally). The coefficient of correlation resulting was +0.13, an insignificant value. On the other hand, between incidence in the 28 boroughs and number of persons per dwelling they did find an appreciable degree of correlation—namely, -0.48—indicating that the more persons per dwelling there were the lower was the attack rate. In explanation the authors suggest that when the virus enters a household it may usually infect all persons but will in most instances produce an overt attack in only one member. It would then follow that the larger the household the smaller on the average would be the proportion of overt attacks.

As an index of social conditions the proportion of persons living more than two to a room would clearly be preferable to the absolute number of persons per dwelling. We have therefore correlated the former with the incidence of poliomyelitis in the London boroughs in 1947, and reach a coefficient of +0.29. This insignificant (and positive) value is in accordance with that found by Daley and Benjamin between the attack rate and proportion of males in the lowest social classes. These correlations for London suffer, it may be noted, from the defect that the indices of conditions are based upon the 1931 census. The relative gradings of the London boroughs may not have undergone serious changes since then, but that is an assumption that must be made.

Summary

It has been suggested that towns with favourable health conditions as revealed by low infant and general mortality rates are peculiarly liable to a heavy incidence of poliomyelitis when that disease becomes epidemic. The recorded notifications of poliomyelitis in the 273 large and small towns of England and Wales show no such association between the attack rates

they suffered in the 1947 epidemic and the infant and general death rate they experienced in the two preceding years, 1945-6. In other words, according to this experience, favourable mortality rates, indicating favourable social conditions in a locality, need not raise fears of an unduly heavy risk when poliomyelitis becomes widespread.

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PRODUCTION OF DENTAL CARIES

A NEW HYPOTHESIS

BY

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Structure of Teeth, with Reference to Occlusal Grooves and Development

Human molar teeth show cusps on the biting surfaces; between the cusps lie grooves. The biting surfaces are known as occlusal surfaces, and the grooves as occlusal grooves. It is of some importance to note that these grooves are commonly the site of caries, especially in the case of the lower first molars. In considering the mode of production of caries the contents of the occlusal grooves must be taken into account, since the grooves themselves are often so narrow that the contents are unlikely to be removed by the chewing of food or the use of a toothbrush. Soon after eruption the contents of shallow occlusal grooves are lost. However, in the present work it is not towards these but towards the narrow inaccessible grooves that attention is directed.

Enamel is laid down by cells (ameloblasts) which move from within outwards, depositing soft enamel matrix, which later hardens to become mature enamel. The passage of the ameloblasts is marked by the traces of organic material which remain between the prisms. The highest concentrations of organic material in enamel are found between the prisms, while the prisms themselves are permeated by organic material.

The enamel can be distinctly seen radiographically only when calcification occurs; this takes place first at the cusp tips and later gradually spreads over the rest of the tooth crown (Applebaum, 1943). Calcification is a late stage in the development of the enamel; finally, the enamel undergoes a process of maturation. Teeth

FIG. 1.—Diagrammatic representation of the order in which calcification occurs in a molar tooth. The formation of an occlusal groove is seen. Drawings based on x-ray appearances. E=Enamel, D=Dentine.

lying under the oral epithelium which are exposed at operation appear on gross examination to be fully calcified; such teeth can also be demonstrated radiographically in this position. There is doubt, however, whether the enamel of such teeth is in every respect fully matured (Professor F. C. Wilkinson—private communication).

On the surface of newly formed enamel there is found a layer of protein (Nasmyth's membrane). It consists in part of the ameloblasts which laid down the enamel and are now lifeless and without further function. Some doubt exists about the origin of the remaining part. Such a layer of protein lines the occlusal grooves, where, if narrow, they are least accessible to wear, but the protein layer is soon worn away from the tooth where it is exposed to mastication, as on the cusps.

A diagram of cusp calcification is shown in Fig. 1. It is not clear whether intact enamel invariably lines an occlusal groove; if the enamel is not intact, direct access to the dentine by mouth fluids and bacteria may occur. Histological examination shows that in some lower first molars the enamel at the bottom of the occlusal groove is faulty at some point or points along its length. Such faults range in size from a minute crack to a gap in the enamel leading to exposure of the dentine. The question arises whether such cracks are developmental or traumatic in origin. King (1935) has produced evidence in favour of the traumatic theory. He examined experimentally the possibility that hard food particles may exercise a "wedging" action in occlusal fissures, and concluded that such an action may play a part in the production of enamel cracks in the molars of rats.

Contents of Occlusal Grooves

Nasmyth's membrane, the layer of protein on the surface of newly formed enamel, is bound down to the surface of the enamel by a series of stalactite-like processes; there is one such prolongation between each enamel prism and its neighbour. Tests have shown that Nasmyth's membrane can resist some though not all forms of bacterial attack. These observations, taken in conjunction with the narrowness of some occlusal grooves, suggest that structures of developmental origin may normally persist throughout life in the less accessible parts of these grooves. Fig. 1 also shows that any tissue which was lying between the cusps as they formed might be "trapped" there and carried through *in situ* when the tooth erupted. Trotter (1941) has shown that fully formed tooth crowns surrounded by formative epithelia may be seen a short distance beneath the oral epithelium before eruption takes place. Although further examination of fissure formation is needed, it seems that some part of the contents of occlusal grooves is developmental in origin—i.e., that part which is situated beyond the reach of normal wear owing to the narrow shape of the occlusal groove.

Examination of buried teeth (which were removed surgically without having been in use in the mouth) shows that two structures which differ in their nature may be found in the occlusal grooves both in unerupted and in newly erupted teeth. These structures are "groove protein" (Pincus, 1948a) and Nasmyth's membrane. It has been possible to separate these two structures and examine them by means of (qualitative) biochemical methods (Pincus, 1948b). Up to now only a few such teeth have been available for examination. While this rigid selection limits the number of specimens, it does ensure that the tissues examined are of truly developmental origin. Nasmyth's membrane, which is one of the two structures found in occlusal grooves, resembles a mucoprotein (see below).

Mucoproteins on hydrolysis yield sulphuric acid, a hexosamine, a hexuronic acid, and acetic acid (Harrow, 1946).

Reference has been made above to the possibility that occlusal grooves with faulty enamel lining may allow direct access of mouth fluids and bacteria to the dentine. This direct channel of communication is of clinical significance because the dentine may thus be exposed to external noxious influences in the absence of preceding caries of the enamel. It should be mentioned, however, that the presence of such direct communication does not necessarily mean that caries of the dentine must occur.

Current Theories of Dental Caries Production

1. Role of Lactic Acid

In 1867 Leber and Rottenstein suggested that caries was due to lactic acid formed from food remnants left on the teeth. Miller (1885) carried out a number of experiments bearing on this question, and the theory has become associated with his name. It is true that lactic acid may be formed as a result of bacterial action. Some lactobacilli are robust organisms, and if present in media rich in carbohydrate they may soon predominate in a mixed culture. In tubes of nutrient broth containing lactobacilli and bread kept at 37° C., to which fresh bread is added from time to time, lactic acid soon accumulates; although such observations as these lend support to Miller's conclusions, facts have since come to light which may affect the validity of the theory.

The conditions in test-tube experiments differ greatly in one respect from those that are present in the mouth; the stasis in the test-tube is in marked contrast to the flow of saliva in the mouth, which can wash away acid that is released. In addition a buffering action is exerted in the mouth by both the calcium salts and the protein present, further minimizing changes in hydrogen-ion concentration. Acid attack on enamel occurs extremely slowly unless the normal pH value of human saliva, which is about 6.8, is replaced by a value below 4.5 and maintained at that level. There is no evidence that a degree of acidity sufficient to produce caries is ever maintained in the *mouth cavity* for the necessary length of time. Soft "plaques" of unknown composition, but probably of bacterial origin, are known to occur on teeth in the mouth, both in areas susceptible to caries and in areas where caries is seldom seen. It has been suggested that these "plaques" are a factor in maintaining a concentration of acid external to the tooth and sufficient to account for the initial lesion of caries; further evidence on this point is, however, desirable.

A further comment on Miller's theory may be made. When a tooth erupts, the occlusal groove, as explained, is filled to overflowing with Nasmyth's membrane and "groove protein" (Fig. 2). In the course of time some of the more superficially situated groove protein is worn away (Fig. 3) and its place may be taken by adventitious material derived from the mouth cavity (Fig. 4). This material may conceivably act as a "plaque"; in other words, it might be a site of lactic acid formation, although, as stated, there is as yet inadequate evidence on this point.

If lactic acid were to be released from this adventitious material and attack the enamel, the site of the resulting caries would be at AA in Fig. 5, on the lateral walls of the *superficial* part of the occlusal groove. In point of fact caries does *not* develop here, but makes its first appearance at the very *bottom* of the occlusal groove—i.e., at B in Fig. 5. Now between the hypothetical site of lactic

acid formation and the actual site of caries development a plug of persistent protein intervenes which would doubtless buffer the acid and protect the deeper part of the groove from being damaged. These considerations suggest that it is highly unlikely that lactic acid formed in "plaques" is the cause of caries beginning at the bottom of the occlusal groove.

These contentions are supported by the following experimental findings. If a perfectly sound molar tooth is placed in a solution of 2% HCl the enamel is in time completely dissolved away, but the protein contents of the groove are left intact. Any lactic acid, therefore, which is formed in a "plaque" in the superficial part of the occlusal groove could not dissolve away the persistent protein content of the groove and thus could not reach the bottom of the groove, where caries actually first sets in. The conclusion is therefore that, whatever may be the role of lactic acid in caries formation in other sites, lactic acid formation cannot account for the development of caries at its commonest site—i.e., at the bottom of the occlusal groove.

FIG. 2.—The occlusal groove in a newly erupted tooth.

FIG. 3.—The occlusal groove in a tooth which has been in use in the mouth.

releases combined acid from the form in which it exists in mucoproteins. Such sulphatase-forming bacteria are present in the mouth as Gram-negative bacilli.

In the present work three sources of sulphatase have been employed—two strains of Gram-negative bacilli found in carious material, and *Aspergillus oryzae*. Material has been extracted from human dentine which when exposed to sulphatase releases sulphuric acid. The sulphatase has so far not attacked intact dentine or enamel protein; the extracted material on which it does act is a polysaccharide in which combined sulphuric acid is present. The dentine protein consists of a protein moiety collagen and the polysaccharide already referred to. Before the sulphatase can act on the tooth it would seem that initial hydrolysis of the protein to release the polysaccharide must take place; it is not known at present how this initial reaction occurs. The presence of a similar polysaccharide has been demonstrated in enamel protein, and there is some evidence that it is also present in groove protein. It is thought that the sulphatase of the Gram-negative mouth bacilli acts on

FIG. 4.—The situation of "plaque" material in relation to groove protein and Nasmyth's membrane.

FIG. 5.—(As Fig. 4.) The arrows AA show where caries might be seen if it followed the breakdown of "plaque" material. Arrow B shows where caries in an occlusal groove is usually found.

2. Relation of Tooth Structure to Caries

The well-known work of Mellanby and Mellanby (1948) demonstrated conclusively that the structure of a tooth depends on the adequacy of the diet in respect of calcium, phosphorus, and vitamin D content. They found, further, that better-formed teeth are less liable to be affected by caries than less-well-formed teeth. The outstanding practical importance of these observations is obvious, but their work does not as yet explain the actual mechanism by which caries is produced in teeth of poor structure.

A Suggested New Chemical Theory of Caries

All previous theories stress the importance of the inorganic constituents of a tooth in relation to caries production. In the new theory to be outlined here it is suggested that the *organic* constituents of a tooth are of major importance. Excluding the cementum and pulp tissue, three proteins are found in teeth—namely, groove protein, enamel protein (Nasmyth's membrane and its prolongations into the enamel), and dentine protein. Dentine and enamel proteins have been examined in some detail, and both have been found to contain combined sulphuric acid. Enamel protein is a mucoprotein (Pincus, 1949). Neuberg and Hofmann (1931) demonstrated that many bacteria can form an enzyme, called sulphatase, which

the polysaccharide in these various tooth proteins, thus releasing sulphuric acid.

It is the initial freeing of combined sulphuric acid that forms the main feature of the present hypothesis. When the acid is freed by bacterial enzyme attack equilibrium is maintained at the expense of the calcium salts. At any given moment of the carious process the only free acid will be that which, having been released from one organic combination, has not yet formed a different combination with the calcium salts. The changes in the organic structures of the teeth are thus regarded as primary and those in the inorganic structures as secondary in the process of caries.

The release of sulphuric acid in enamel and in dentine may be expected to produce different effects on these two tissues as shown by experiments in which enamel and dentine were exposed to acid. Enamel attacked by acid becomes friable and is easily lost, while dentine attacked by acid may remain little changed on gross examination, apart from becoming softened. This difference in behaviour is accounted for by the fact that the inorganic material in enamel and in dentine may amount to 95% and 75% respectively. Thus the enamel exposed to acid will lose up to 95% of its constituents, while the dentine will lose only 75%, leaving an adequate organic framework to maintain its general arrangement.

It is important to note that in clinical caries a similar state of affairs is found—i.e., the enamel is friable and readily lost, while the dentine is softened. It follows from the hypothesis enunciated above that CaSO_4 should be present in carious material as a result of the interaction of the released sulphuric acid with calcium phosphate. In fact, CaSO_4 has been demonstrated in carious material, and it is absent from sound tooth structure.

Gram-negative sulphatase-producing bacilli would thus be the ultimate cause of caries. We do not yet know what are the conditions which determine the production and activity of the enzyme by these bacilli. Such conditions may play a large part in precipitating or preventing caries. This hypothesis argues that any organism in the mouth which can release sulphatase may be a factor in the production of caries. In other words, caries is not due to a specific bacillus but to specific enzymes, one of which has already been demonstrated, though obviously enzymes other than sulphatases are also involved in the complex process of initiation of caries.

The conditions at the bottom of an occlusal groove would seem to be favourable for the multiplication of the Gram-negative bacilli and the release and action of the sulphatase and other necessary enzymes. If the enamel were first attacked this would enable the organisms to penetrate into the dentine. Although the organisms might initially enter the dentine through a minute site of destruction in the enamel, once they had got into the dentine they could further damage the enamel from its deeper aspect.

The question still remains to be answered whether the hypothesis enunciated above can account for caries in situations other than the bottom of the occlusal groove. CaSO_4 has been demonstrated in carious material no matter what the site from which it has been obtained, provided enough material is available. In other words there is an *a priori* reason for supposing that sulphatase-forming bacteria may be concerned in caries production anywhere in a tooth.

Experimental Details

Organic Material Present in Enamel and Dentine.—Protein is found on the surface of newly erupted enamel (Nasmyth's membrane) and permeates the enamel in the form of threads, one such between each enamel prism and its neighbour (Fig. 6). The presence of organic material

FIG. 6.—Diagram illustrating the distribution of tooth proteins.

in enamel can easily be demonstrated. After a thin slice of enamel has been slowly attacked by a weak acid so that most of the inorganic matter passes into solution, microscopical examination shows fine strands of an acid-resistant nature which remain *in situ*, leaving a replica of the structure of the enamel, though this is now made up of organic material. Histological examination suggests that the organic material is a mucoprotein. In the present work sections of developing human enamel have been stained with thionin, when material resembling mucin was seen (Pincus, 1948c). Wislocki *et al.* (1948), using histochemical methods, found that the ground structure of the enamel organ resembled an "epithelial mucus," comparable in staining reactions to the acid mucopolysaccharides of some con-

nective tissues. Chemical examination of the organic material has shown it to be a mucoprotein. Its chemical composition is: nitrogen 5.1%, sulphur 0.4%, hexosamine 11.2%; while the following qualitative tests are positive: Millon, xanthoproteic, Sakaguchi, ninhydrin, *p*-dimethylaminobenzaldehyde, naphthoresorcinol, carbazole (Dische, 1947).

Mucoproteins and Chondroitin Sulphuric Acid.—Few direct observations on the amount of protein present in enamel have been made. As a rule, determinations of nitrogen are carried out and the amount of protein calculated from these results. Since mucoproteins contain a lower percentage of nitrogen (10%) than do other proteins (15%), it will be clear that the actual amount of protein present in enamel may be 50% greater than has previously been supposed. To arrive at a result more directly, the protein must first be separated from the enamel, a matter of some difficulty. This point is emphasized to show that the amount of protein present in enamel is sufficient for the production of acid as demanded by the new theory, and may amount to 5% by volume. It is known that dentine contains collagen (Harrow, 1946), and I have demonstrated that dentine contains the polysaccharide chondroitin sulphuric acid, which may be separated from dentine by the use of a method similar to that employed to separate the polysaccharide from cartilage (Meyer and Smyth, 1937). The composition of chondroitin sulphuric acid separated from dentine is: nitrogen 1.7%, sulphur 4.6%, acetyl 8.1%, hexosamine 26.3%, hexuronic acid 28%.

Caries Bacteria

In earlier work (Pincus, 1948d) I have shown that, when mixed caries bacteria were inoculated into tubes containing cartilage (which is rich in chondroitin sulphuric acid) and incubated at 37° C., first Gram-positive forms resembling enterococci grew, while, later, Gram-negative bacilli resembling those of the *Proteus* group eventually outgrew all other forms. Both the Gram-positive and the Gram-negative forms were classified by their characteristics as shown in pure culture. Now, Gram-negative bacilli of the *Proteus* group are found in caries (Hine and Bibby, 1939); Neuberg and Hofmann (1931) have demonstrated in Gram-negative bacilli of the *Proteus* group the presence of an enzyme (sulphatase) that can liberate sulphuric acid from organic compounds in which it is present in combined form—e.g., mucoitin and chondroitin sulphuric acid. I have suggested above that such bacilli are present in the mouth and may play a part in caries by releasing sulphuric acid from the organic compounds in which it exists in the teeth. Evidence is presented elsewhere that bacterial enzymes can release free sulphuric acid quantitatively from both chondroitin and mucoitin sulphuric acid, which can be split off from enamel and dentine proteins.

It may be seen that caries of enamel and of dentine may be accounted for by the hypothesis set out above, for which there is some experimental support. The fact that a large mass of carious dentine is often found in a tooth despite the tiny size of the point of entry in the enamel is a clinical commonplace for which the present hypothesis offers a reasonable explanation. In the new theory, once suitable organisms gain access to the dentine bacterial growth and enzyme production may proceed, using as nutriment that available in the tooth itself. No nutritional factors other than these would then be needed.

Summary

Between the cusps of molar teeth lie grooves which, especially if narrow, are a common site of caries. These grooves in newly

erupted teeth contain two structures which differ in biochemical nature; one is a mucoprotein.

Enamel at eruption is covered with a layer of protein, and is permeated with protein throughout life. Enamel protein is a mucoprotein, which comprises a class of proteins containing mucoitin sulphuric acid.

Dentine contains chondroitin sulphuric acid.

Gram-negative bacilli found in caries can release an enzyme—sulphatase.

Sulphatase can release sulphuric acid from such combined forms as mucoitin sulphuric acid and chondroitin sulphuric acid, thus attacking the calcium salts of both enamel and dentine and causing caries.

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A CASE OF PSITTACOSIS TREATED WITH PENICILLIN

BY

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The purpose of this note is to report the case of a patient infected with psittacosis who responded to treatment with penicillin.

Case History

A medical research worker aged 43 was admitted to hospital on Sept. 14, 1948. His work during the previous three months had involved the handling of material obtained from mice infected with psittacosis virus.

Two weeks before admission he had developed severe coryza. Six days later (eight days before admission) he suffered the sudden onset of marked malaise, shivering, and high fever (temperature 103° F.—39.4° C.) associated with severe headache and vomiting. He went to bed, and the symptoms persisted unchanged for 48 hours. Then they suddenly abated, and for 12 hours he felt much better. But five days before admission fever, rigors, headache, and vomiting returned; anorexia was complete; both mental and physical prostration soon became marked features; and he slept poorly or not at all. He developed a slight cough producing only scanty sputum. The day before admission he developed a sore throat.

On admission to hospital he looked seriously ill, with pale complexion, sunken eyes, and hollow cheeks. His lips were crusted with sordes, and his tongue was dry, brown, and furred. He was not dyspnoeic, and lay flat in bed without distress. His temperature was 99° F. (37.2° C.), pulse 80, and respirations 22. The fauces and tonsils were injected but no exudate

was seen. The right tonsillar gland was enlarged and tender, but other lymphatic glands were normal. Bronchial breath sounds were audible in scattered areas over the right lung base posteriorly, and there were crepitations on inspiration in this area. The cardiovascular system was normal and the blood pressure 100/70 mm. Hg; the spleen was not enlarged. The central nervous system was normal except for the profound mental prostration. Questions were answered reluctantly, slowly, and with difficulty, but the answers were nevertheless clear and not confused.

Laboratory Investigations.—On Sept. 14 a radiograph of the chest revealed loss of translucency in the right lower zone, suggesting an inflammatory lesion. A psittacosis complement-fixation test was positive to a titre of 1/64. The titre rose to the level of 1/256 on Sept. 27. Blood culture was sterile aerobically and anaerobically. A throat swab revealed no haemolytic streptococci, diphtheria bacilli, or Vincent's organisms. On Sept. 15 a blood count showed: Hb, 89%; white cells, 5,400 per c.mm. (polymorphs 84%, eosinophils 1%, lymphocytes 10%, large hyalines 5%). Sputum contained many bacteria and some monilia, but no virus was seen. On Sept. 21 a radiograph of the chest showed that the lower zone of the right lung field had cleared. An irregular opacity was apparent in the left mid-zone. On Sept. 27 the lung fields were clear.

Treatment.—The history of exposure and the clinical features of the illness made the diagnosis of psittacosis certain enough to justify treatment before laboratory confirmation was available. Apart from penicillin, the only drugs used were analgesics to relieve headache and sedatives to ensure sleep. Each dose of penicillin was mixed with 1 ml. of 2% procaine to reduce the discomfort of the injection. Penicillin therapy was started in the patient's home on Sept. 13, seven days after the onset of the illness. On that day 1,200,000 units were given in three doses. On Sept. 14, the day of admission, one dose of 500,000 units and one of 1,000,000 units were given. Thereafter 1,000,000 units of penicillin were injected twice daily for four and a half days. The drug was discontinued on Sept. 19, the patient by then having received a total of 11,700,000 units.

The response to treatment was most satisfying. On Sept. 16, ten days after the onset of the illness and 72 hours after the initiation of penicillin therapy, the patient was completely apyrexial (see Chart), his mental processes were noticeably

clearer, and he was sleeping well. Next day the signs of consolidation at the base of the right lung were still present, and in addition there was clinical evidence of left basal pneumonia. These fresh pulmonary findings were not, however, accompanied by further symptoms or constitutional upset. On Sept. 19 treatment with penicillin was discontinued. On Sept. 21 a radiograph of the chest confirmed the clinical findings by showing diffuse shadowing at the left mid-zone, suggesting an inflammatory process. But by now the right base showed considerable clearing radiologically. Clinical improvement was rapid, and on Sept. 27 the lungs were normal both clinically and radiologically.