that the infective agent could be filtered, and his work was confirmed by others, the usual incubation period being one to eight months, probably depending upon the susceptibility of the individual. Filtrates from condylomata acuminata were also found to be infective. Immunity to the virus has been demonstrated, and its spontaneous development probably accounts for the sudden disappearance of lesions. Acidophilic bodies in the cytoplasm and basophilic ones in the nucleus of affected cells have been described as inclusion bodies. Histologically there is evidence of active proliferation of cells in the Malpighian layer, resulting in the formation of a surface projection and in elongation and widening of the interpapillary processes, with thickening of the stratum corneum. The amount of cellular infiltration and inflammatory reaction varies widely, and is most marked in the case of moist warts. It is probable that the clinical varieties enumerated depend upon the following variable factors:

1. The reproductive activity of the germinal layer.
2. The degree of acanthosis.
3. The degree of corneous hypertrophy.
4. External influences such as pressure, humidity, and friction.

CONCLUSION

I am aware that there are many omissions in this brief paper, and I have not mentioned the effects of physical and chemical agents upon viruses, nor have I discussed general problems of immunity. With regard to the latter it is perhaps worthy of remark that there is no real difference between viruses and bacteria. In other words, the immunity which follows recovery from virus infections is just as variable between diseases as that following bacterial infections.

To conclude, I would like to associate myself with Goodpasture when he deplores the abuse of the group of virus diseases as a repository for all sorts of nondescript and ill-defined conditions of unknown aetiology and indefinite pathology. There are a number of common dermatological conditions the origins of which are completely obscure, and naturally the viruses are suspect. However, since Pasteur's suggestion more than fifty years ago that some diseases might be due to ultra-microscopic organisms, there is no originality of thought in incriminating a virus without supporting evidence.

I am very happy to acknowledge my indebtedness to the London Hospital for the research facilities and the financial assistance its Research Fund Committee has so generously afforded me. I have been working on certain aspects of virus diseases under the direction of Dr. S. P. Bedson in the Freedom Research Laboratory of the London Hospital since November, 1930, and my acquaintance with these problems and my few contributions to the solution of some of them are alike due to much instruction and expert help from Dr. Bedson. I record these facts because they account entirely for my present part in this discussion, and for these reasons I regard the implied distinction as something impersonal.

In composing this paper I have drawn largely from the volume on virus diseases produced by the Medical Research Council and also from the excellent paper by Goodpasture on cellular inclusions and the aetiology of virus diseases. The numerous references given in these two sources are omitted from the list below.

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NASAL GRANULOMATA*

BY

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Tumours mainly composed of granulation tissue may occur in any region of the body. They are not commonly met with in the nasal cavities, but certain varieties, when present, are of great interest to the rhinologist. From the point of view of histology their general structure is always broadly the same, though certain differences in detail may be present, which will depend on the aetiology of the tumours. According to Baum¹ all granulomata present "collections of rapidly growing blood vessels whose walls are formed by a single layer of epithelium supported by a stroma of young connective tissue containing many cells." In addition, however, the growth may present a specific or infective organism, which will definitely decide the nature of the tumour.

For the purpose of this discussion I shall first describe granulomata which show no specific organism to either histological or bacteriological examination. This class, which in structure corresponds most closely to pure granulation tissue, may be divided into two groups—simple and malignant.

SIMPLE GRANULOMA

Tumours of the first, or "simple," group may be met with in any part of the body; when occurring in closed cavities such as the abdomen or thorax they may grow to a huge size and closely resemble malignant growths in their behaviour and appearance. Prima² reports five such cases, three in the abdominal cavity, one in the thorax, and one on the back; owing, however, either to their enormous size or to their position complete removal was impossible, and treatment had to be confined to partial excision and packing. Histological examination showed these growths to be what he termed "chronic inflammatory granulomata," and it is of much interest that in each case the growth completely disappeared as a result of the operative intervention. Very extensive simple granulomata are not met with in the nasal cavities, for the reason probably that they produce symptoms which draw attention to their presence at an early date. When occurring they are usually due to trauma or the presence of a foreign body.

In the first instance they are most often post-operative, while in the second any of the more common varieties of foreign body may, as a result of inflammatory changes, become surrounded with granulation tissue to such an extent as to form a true tumour. Pearlman and Pilot³ report such a case, caused by strands of gauze which had remained in one side of the nose for a period of two years. They point out that granulomata due to foreign bodies often resemble polypoid growths, and have a distinct inclination to myxomatous changes. Giant cells with an enormous number of nuclei are usually found in the neighbourhood of the irritant. The diagnosis and treatment of such growths are not usually difficult.

MALIGNANT GRANULOMA

In the year 1896 McBride⁴ published a case of "rapid destruction of the nose and face in a young man of 28." It started as a pustule on the inside of the ala nasi, following a scratch from a finger-nail. The disease manifested itself as a steadily progressive phagedaenic ulceration, which resisted anti-syphilitic treatment and caused the death of the patient some nine months later. Histological

* Read in opening a discussion in the Section of Oto-rhinolaryngology at the Annual Meeting of the British Medical Association, Dublin, 1933.

examinations of removed tissue gave a negative result, and the necropsy threw no light on the subject. This is the first reference I can find to any case which will fit in with the two following, fully described by Woods⁵ in the year 1921.

Woods states that these cases were unique in his experience, and as a suitable name he suggests "malignant granuloma." They both occurred in elderly men, and presented the typical appearance of tertiary syphilis—feter, which was of a quite peculiar nature, glutinous crusts, perforation of the septum, and a steady, progressive necrosis of the bony framework of the nose and palate. In each case the Wassermann reaction was negative, and anti-luetic and local treatment was of no avail. Microscopical examination showed granulation tissue to be the dominant feature.

In the first case α -ray treatment was carried out, but without improvement, and this patient died from cachexia four and a half years after the onset of the disease.

The second case closely resembled the first, and as anti-syphilitic treatment was here also of no benefit, it was decided to try the effect of radium emanation. This was introduced through a perforation in the palate; four tubes of 12 millicuries activity, in steel needles wrapped in tea lead, were used, and as a result great improvement took place at the end of two weeks. A second dose of 20 millicuries was then given, and this was followed by rapid healing. A small recurrence on the inner wall of the left nose was similarly treated, and the patient left hospital apparently cured. StClair Thomson⁶ states that he has observed two similar cases, one male and one female.

These cases, then, represent a type of granuloma which, though simple in that no organisms or histological abnormalities were found, were nevertheless definitely malignant in their course. Woods sums up the cases as follows: "Until we understand what is meant by a cell taking on malignant action we cannot doubt that what happens to one kind of cell may happen to another, and if we can have a malignant epithelioma why not malignant granuloma?"

I do not find any further reference to this class of tumour until 1925, when McArthur⁷ of Melbourne published an almost similar case. Here again tertiary syphilis, despite a negative Wassermann, would not be denied as a diagnosis, and once again the disease refused to be affected by the most energetic anti-syphilitic treatment. McArthur, who grasped the similarity of his case to those reported by Woods, employed radium (in what form he does not state) as a therapeutic measure; as there was, however, no apparent effect, three full doses of α -ray therapy were given. Improvement followed, the necrotic areas came away, healing took place, and there was no return of the disease one year later. Here again no organism could be isolated; granulation tissue formed the principal mass of the growth, and the author considered the case to be one of malignant granuloma.

I find no further reference to this variety until the year 1929, when Kraur⁸ published notes of three cases which, in my opinion, might be included in this group. His communication was a provisional account of the results of morphological examination of a peculiar and hitherto undescribed lesion of the nose, mouth, and pharynx. Details of three cases are given, all of which occurred in men. They differed somewhat from the cases reported by Sir Robert Woods, by starting in the soft tissues—two in the anterior nares and one in the soft palate.

In each case the disease showed the same tendency to spread, but without definite tumour formation. Eventually the nasal cavities, alveoli, and palate were infiltrated, and from the description given these cases appear to have resembled very closely malignant granulomata. As a

result of histological examination the author believed that, certainly in two of his cases, he was dealing with an independent specific process of a chronic inflammatory nature but of unknown aetiology. In the third case he considered that he may have been dealing with a granuloma with sarcomatous changes. Because of the destructive effect in parts of the described granulomata, attributable to the presence of gangrene, he suggests that the clinical picture might be described as "granuloma gangrenescens." The particular treatment adopted is not described, but one patient died from secondary haemorrhage five and a half months after the onset of the disease, the other two from cachexia.

The last and most recent case I have found in the literature is reported by Dr. Geo. B. Wood.⁹ He terms it "a case of mutilating granuloma of the nose and face with fatal ending." The patient was a female aged 32, and the disease began with soreness and swelling of the tip of the nose, accompanied by rather profuse watery discharge. On examination the septum was found perforated, and there was extensive crusting and swelling of the floor of the nose. The condition suggested tertiary syphilis and, in spite of a negative Wassermann and negative therapeutic results, a provisional diagnosis of a breaking-down gumma was made, and active anti-syphilitic treatment was given. This had no effect, and the disease made steady progress, involving the cheeks on both sides, until finally, at the time of her death, practically all the structures between her eyes and lower jaw had become involved. She died from cachexia, having lived for about twelve months from the time she first came under observation. Very full and careful bacteriological and histological examinations were made by several pathologists, and as a result no more definite name could be given to the growth than that of "granuloma of a malignant type." There is no mention of either radium or α -ray therapy having been employed.

I have dwelt in some detail with these cases; there are very few on record, and it would seem that recognition must be given to a tumour of unknown aetiology, due to no visible organism, made up of granulation tissue, and malignant in its behaviour. It would be interesting to know if any similar growths have been described in other regions of the body.

CARCINOMA AND SARCOMA

Though, strictly speaking, carcinoma and sarcoma do not belong to the granuloma group, they must always be thought of when the question of diagnosis arises. Primary carcinoma is rare, while sarcoma is not so uncommon. Carcinoma when present is usually a squamous-celled epithelioma, and may occur at the junction of skin and mucous membrane, but is also met with in any part of the nasal fossae. Sarcomata are usually of the round or spindle-celled variety; "of eighty tumours of the septum tabulated by Arslan,¹⁰ twenty-nine were cases of sarcoma and eleven carcinoma."

GRANULOMA OF SPECIFIC INFLAMMATORY ORIGIN

There still remain for discussion granulomata due to a specific inflammatory condition. This group will include:

- (1) Syphilis. (2) Tuberculosis. (3) Glanders. (4) Leprosy. (5) Actinomycosis. (6) Rhinoscleroma.

The syphilitic granuloma or gumma is too well known to require description. Suffice it to say that, when occurring in the nose, it is most frequently seen on the septum, where it may produce large perforations of either the cartilaginous or bony portions.

Nasal tuberculosis is an extremely rare condition and is usually secondary. The tuberculous tumour varies from small nodules the size of a pin's head to those as large

as a pea. The histology resembles that of the tuberculous lesions in other situations; only identification of the tubercle bacillus in either the growth or discharge can definitely decide the nature of the disease. In connexion with tuberculomata may be mentioned the allied disease lupus. When primary, the septum is the favoured situation, but the turbinates also are almost invariably attacked as the disease advances. The progress of lupus in the nasal cavities resembles that in other regions, and as a rule the diagnosis is not difficult.

Glanders, leprosy, actinomycosis, and rhinoscleroma are only mentioned to complete the list of possible granulomata. They are to be thought of in the absence of the more common form of tumours. Leprosy and rhinoscleroma are so rare in this country as to be scarcely worth considering, while glanders and actinomycosis can be only definitely established by the finding of their specific organisms.

In this communication I have only touched on most of these diseases. To deal with the nasal granulomata from all points of view would absorb more time than is at my disposal. If, however, I have succeeded in stating a sufficient number of facts to promote a discussion, then my object will have been more than achieved.

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Memoranda

MEDICAL, SURGICAL, OBSTETRICAL

THE ORIGIN OF PULMONARY TUBERCULOSIS: MUTATION OF TUBERCLE BACILLI

It has always been impossible to explain why the overwhelming amount of primary pulmonary tuberculosis should occur in human beings between the ages of 16 and 26. I venture to suggest that living bovine bacilli swallowed by an infant with milk are conveyed to the mesenteric glands, where they lie dormant in a new environment—namely, human tissues—and are conveyed to the lungs before or after mutation into living active human tubercle bacilli. In the *British Medical Journal* of February 27th, 1932, I suggested the possibility of mutation of the tubercle bacillus from the bovine type to human type after a long residence in human tissues, and quoted the case of a farmer who had recovered from tuberculous glands in the neck when 5 years old. Forty years after, he developed pulmonary tuberculosis; the tubercle bacilli found in the lung were human, while those found in the neck glands were presumably bovine. It is extremely difficult to obtain proof of this theory, as the interval between the primary infection and the later one is usually fifteen to twenty years. I have had the good fortune to observe the following case, which I reported to the Royal Society of Medicine fully in February, 1914, and which, by the courtesy of Dr. Dunderdale, I have recently examined in detail. Briefly, the case is as follows:

Twenty years ago a girl developed tuberculous adenitis of both sides of the neck, with tuberculous small joints of hands, and rheumatism. The glands suppurated and were

drained, as it was impossible to excise them. At this time there was no evidence of pulmonary disease. She was treated with injections of tuberculin, and made a good recovery. Examinations of the pus and glands and animal inoculations showed definite *bovine* tubercle bacilli. Eighteen years after the glands in the neck had subsided, she developed pulmonary tuberculosis in both lungs. Cultural and animal examinations show the bacilli to be human in type.

This is the first opportunity I have had of producing some scientific proof of my belief that pulmonary tuberculosis may be caused by the ingestion of bovine bacilli in infancy: that these bacilli are conveyed to the lungs, where they lie dormant for many years, and in a new environment undergo mutation into human bacilli and so cause pulmonary tuberculosis. If this is correct, it would account to some extent for the great mass of cases of this type occurring between the ages of 16 and 26.

Sir William Whitla, in his brilliant Cavendish Lecture in 1908, has shown that living tubercle bacilli introduced into the stomach of an animal are to be found in four hours in the lung substance, and that the bacilli can pass rapidly through the intact intestinal mucosa without producing any local lesions. Calmette has shown that if the oesophagus is ligatured carbon particles cannot reach the lung after inhalation. These facts go a long way to prove the theory which I have always held—namely, that pulmonary tuberculosis is not caused by inhalation, but by the ingestion of bacilli, which penetrate the intestine and are conveyed by the thoracic duct to the lung. The importance of this cannot be exaggerated when we come to consider the prophylaxis of pulmonary and other forms of tuberculosis. By a blind adherence to the inhalation theory the part played by the intestine has been minimized, whilst an infected milk supply has been permitted to inflict its ravages on the human race (Whitla). The amount of tuberculosis in dairy cows in this country is alarming, and to-day about 10 per cent. of milk sold to the public contains living tubercle bacilli. If this serious state of things could be remedied by compulsory pasteurization in my opinion the whole of surgical tuberculosis would be eradicated from children, and also a fair proportion of pulmonary tuberculosis.

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PLACENTA PRAEVIA WITH TWIN PREGNANCY AND ADHERENT PLACENTA

Placenta praevia with a twin pregnancy must certainly be rare, and as the treatment presents certain points of special interest no further excuse is necessary for placing the following case on record.

A multipara, aged 27, was admitted to the hospital at 12.55 a.m. on May 19th, 1933. She was twenty-eight weeks pregnant, and bleeding from the uterus had commenced about midday on May 18th, twelve hours prior to admission. When I saw her the skin was blanched, lips a pale pink, pulse of moderate volume and rate below 100, and the temperature subnormal. She was still bleeding, and abdominal palpation gave no definite information. On vaginal examination the cervix admitted two fingers, and the internal os appeared to be completely covered by placenta.

A general anaesthetic was given at 1.15 a.m., and I performed bipolar version (after Braxton Hicks's method) and brought down a leg. It was unnecessary to go through the placenta, since at one point it was possible to reach and rupture the membranes without disturbing the placenta overlying the internal os. The procedure took two minutes, and little manipulation was necessary, as a knee was soon palpated with the finger-tips on rupture of the membranes. The patient