causing malignant granulomata. In an attempt to isolate a virus I have injected a series of laboratory animals with a bacteria-free extract taken from two cases of malignant granuloma. Those animals that were not killed for examination looked extremely healthy and produced bigger and better litters than some of their colleagues not partaking in the experiment. All the killed animals were found to be healthy. Many organisms have been found in cultures grown from pus in cases of malignant granuloma. It may be significant that it has been a staphylococcus in 89% of cases, whereas in purulent maxillary sinusitis only one-third of cases grow staphylococci.

(3) *Urinalysis:* Red cells, casts and albumin may indicate involvement of the kidneys.

(4) *Blood count:* Very little can be learned from the red and white cell counts. There is often a microcytic anæmia, probably due to toxic absorption and small hæmorrhages. A noticeable feature of this disease is the unexpectedly poor white cell response associated with such widespread destruction. An eosinophilia is present in many but by no means in all cases of periarteritis nodosa. If found, it adds weight to a diagnosis of periarteritis. The sedimentation rate gives information of a general character; it is a measure of the presence and intensity of morbid processes within the body and, for example, reflects the intensity of tuberculous infections more accurately than many other guides. During the height of the disease, in cases of malignant granuloma, the ESR is unusually high, the fall after treatment coinciding with improvement in the patient's clinical condition. In simple maxillary sinusitis and malignant disease of the nose and paranasal sinuses the ESR is not raised, whereas in practically every recorded case of malignant granuloma, where it has been estimated, it has been elevated to a considerable degree.

It has been known for a long time that a high sedimentation rate is usually due to an increase in the concentration of fibrinogen, or globulin, or both. It was because of this that ten years ago I estimated the serum proteins by the normal salt fractionation method and by electrophoresis in a case of malignant granuloma. It was found that the increase in globulin level closely followed the rise in the ESR. Flynn (1954) stated that the γ-globulin was increased in chronic infections, liver disease and collagen disease, and that the most notable and consistent feature in collagen disease, even in the early stages, was a considerable increase in the γ-globulin. Periarteritis nodosa is one of the conditions classified as a collagen disease.

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Mr Alan P Ardouin
(*Charing Cross Hospital, London*)

The Management of Malignant Granuloma

Although 'malignant' granuloma has been recognized since McBride described his case in 1897 the treatment and general management of patients with this disease has been as varied as the theories of its causation. The evidence within the last decade (Friedmann 1955, Mills 1958) has shown that it is a manifestation of hypersensitivity. With this knowledge the results of treatment have been slightly encouraging.

The cases described below are grouped into the three categories suggested by Walton (1959): (1) Classical midline granuloma or Stewart type (Stewart 1933). (2) Giant cell granuloma or Wegener type (1939). (3) Those lesions which mimic the above but have a true neoplastic basis, usually reticulum cell sarcoma. This group is included to illustrate the difficulties in differentiating these cases from those of true malignant granuloma (Burston 1959, Hultberg *et al.* 1957).

In the management of malignant granuloma the correct diagnosis, specific treatment and after care will be considered.

Stewart Type of Granuloma

The mode of presentation of this type of granuloma is typical. Before the disease becomes manifest there is a prodromal stage suggestive of vasomotor rhinitis. Both cases in this category show this.

Case 1

Male, aged 49. Motor mechanic

In November 1955 he attended out-patients with a six-week history of watery nasal discharge, pain in the right cheek and soreness in the right side of the nose. His practitioner had been treating these symptoms with sulphonamide nose drops and short-wave diathermy without effect.

An ulcerating, granulomatous lesion was seen involving all the right inferior turbinate. It extended upwards as far as the hiatus semilunaris and down on to the floor of the nasal fossa. The skin of the vestibule was also affected, but there was no external ulceration of the face.

An X-ray of the sinuses showed mucosal thickening in the right antrum. Chest X-ray clear, WR negative. A biopsy was reported as showing nonspecific granulation tissue; a further specimen was examined a week later and, in consideration of the evidence both clinical and histological, the pathologist agreed that the appearances were consistent with malignant granuloma.

Because of the successes of Glass (1955) and Howells (1955), the patient was treated with small doses of radiotherapy; he received six treatments in twenty days to a total dose of 300 r.

The ulcer healed two weeks after the completion of treatment. Three months later, however, he had a local recurrence on the remains of the inferior turbinate. This was treated with further radiotherapy, 900 r over six treatments in three weeks. The lesion healed rapidly and there has been no recurrence. He was quite well when last seen in January 1963.

Case 2

Female, aged 49

This patient had a lesion almost identical to that of Case 1. She came to us in August 1963, complaining of a watery, blood-stained discharge from the left nostril. The whole of the inferior turbinate was affected by necrosis. There was no evidence of any systemic disease in that her ESR, chest X-ray, plasma proteins and urinalysis were normal. Although the rest of her nasal cavity appeared healthy there was evidence of angiitis in the vessels of the adjacent middle turbinate.

Treatment as for Case 1 has been given and her nose has healed although it is too soon to claim a cure.

Both these patients had early disease and the results of their treatment confirm the benefit from small doses of radiotherapy. It may be that these small lesions would have responded to steroids. The advantage of low dosage is that radiotherapy may be repeated (Glass 1955).

Wegener Type of Granuloma

The diagnostic criteria of Wegener's granulomatosis (Godman & Churg 1954) are: (1) Necrotizing granuloma of the upper and/or lower respiratory tract. (2) Generalized focal necrotizing vasculitis. (3) Glomerulitis.

This, however, is the final picture of a progressive disease which, although it may present with a solitary manifest lesion, shows evidence of its generalized nature from the start.

Case 3

A woman aged 45 complained of a runny, stuffy nose for many years. At the end of 1962 she noticed an increasing nasal obstruction. She was put on the waiting list at her local hospital for a submucous resection of the nasal septum.

During the following three months she noticed a change in her nasal contour (Fig 1): there was a falling in just below the bridge so that it looked like a boxer's nose.

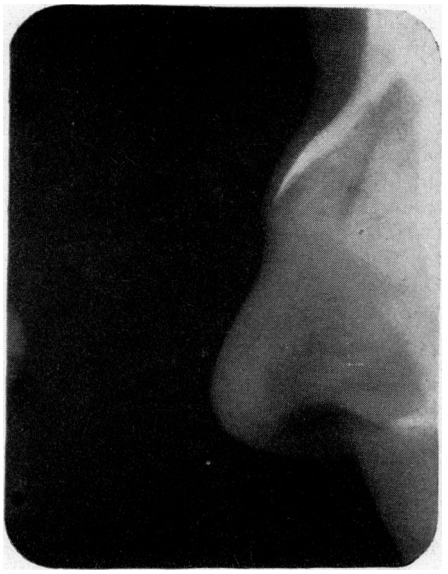

Fig 1 **Case 3** *Soft tissue X-ray showing collapse of nose*

She was referred to Mr Lionel Taylor who noticed that the cartilaginous septum bulged into both nasal cavities resembling an abscess. On exploration this swelling was found to be a friable mass of pale tissue. The septal cartilage was absent.

Histology of this tissue showed necrotic granulation tissue with scattered giant cells – malignant granuloma of the Wegener type. There was little evidence of any generalized disease except that her ESR was 30 mm in 1 hour (Westergren) – rather more than would be expected for a lesion of this size.

On this evidence alone it was decided to treat her with steroids. Prednisolone 10 mg four times a day was given for a week and then reduced gradually over the next three weeks to a physiological dose of 2·5 mg twice a day. The response was dramatic. Within the first ten days the swelling subsided completely and the site of the biopsy had healed. We are keeping her on her small dose of prednisolone for the time being.

The next two patients are unusual in that they came to us with ear disease and it took some while to arrive at the correct diagnosis.

Case 4

An Indian from East Africa, aged 21, came to this country in November 1959. In June 1960 he was admitted to his local hospital with a febrile illness. He complained of a cough, joint pains and epistaxis. No cause for these symptoms could be found. The only finding was a diffuse coarse shadowing in both lungs. Exhaustive investigations for tuberculosis, sarcoidosis, rheumatoid arthritis, lupus erythematosis, typhoid and brucellosis were negative. Nor did virus studies help.

His pyrexia subsided with chloramphenicol but there was no change in the lung picture.

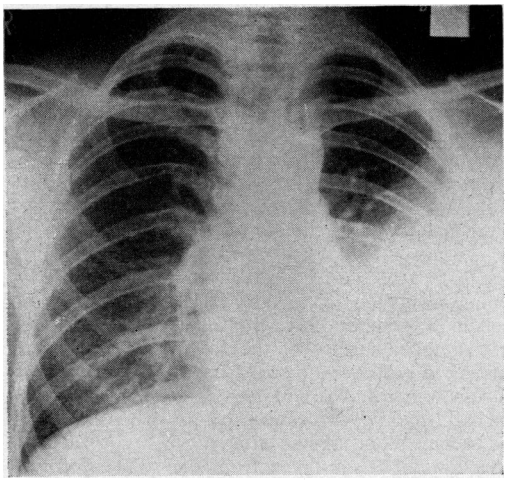

Fig 2 **Case 4** *Lung shadowing and left pleural effusion (11.12.60)*

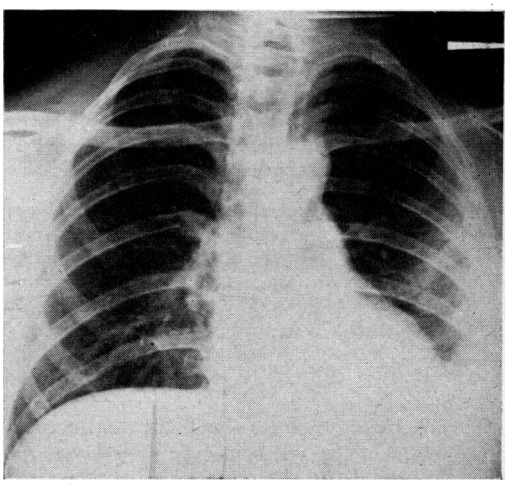

Fig 3 **Case 4** *Lung shadowing less marked after prednisolone therapy (18.1.61)*

On 24.11.60 he was readmitted with an exacerbation of his symptoms and a painful discharge from the right ear; there is no record of the state of his ears at the previous admission but he gave no history of past ear disease. Because his ear became more painful he was transferred to Charing Cross Hospital on 9.12.60 and mastoidectomy was performed the next day.

At operation the right mastoid was found to be cellular and full of necrotic granulations. This was reported as non-specific granulation tissue by the pathology department. The next day the patient's temperature rose to 103°F and a left pleural effusion was aspirated (Fig 2). The fluid was clear and contained red cells and a few lymphocytes. A further aspiration was performed on 14.12.60 and a litre of heavily blood-stained fluid was aspirated. A pleural biopsy was taken and this showed granulations and scattered giant cells. The architecture was quite unlike tuberculosis (subsequent guinea-pig inoculation was negative). A diagnosis of Wegener's granuloma was suggested. This was further supported by a raised serum γ-globulin, and red cells and protein in the urine. The blood urea was normal.

Prednisolone 15 mg four times a day was given and the temperature fell to normal in twenty-four hours. By 18.1.61 the shadowing in the chest was much reduced (Fig 3). The mastoid wound healed well.

During treatment a transient papular rash appeared for five days but did not develop into vesicles. The prednisolone was gradually reduced after one month and finally stopped on 23.2.61 after stimulating normal adrenal function with ACTH.

Case 5

This patient's case has already been published by Symmers (1960). She was an American school teacher on a lecture tour of this country during the summer of 1957. On the voyage she developed an influenza-like illness and pain in the right ear. She attended hospital in Scotland where a diagnosis of acute otitis media was made. Penicillin was prescribed. Before she had completed the course her tour took her south to East Anglia where she was advised to continue the penicillin.

We saw her a few days later on 20.7.57. She was obviously ill with a high, swinging fever and mastoiditis. A cortical mastoidectomy was performed on 24.7.57. The cells were filled with pus and granulation tissue thought to be typical of the acute infection modified by antibiotic therapy. The histology of this material was reported to be partially necrotic non-specific granulation tissue.

There was no improvement in her condition and on 28.7.57 multiple shadows appeared in the lungs (Fig 4). These were mistaken for pyæmic infarcts. Her blood urea was 39 mg/100 ml and the urine normal. On 9.8.57 an exploratory laparotomy for a swelling in the left loin failed to substantiate a perinephric abscess.

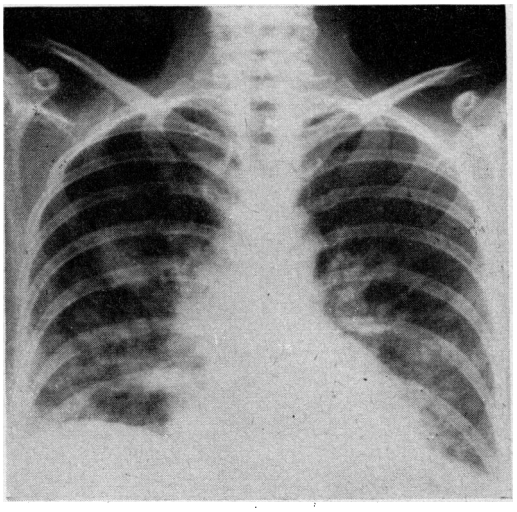

Fig 4 **Case 5** *Granulomata in lungs prior to therapy (28.7.57)*

A little blood-stained fluid was seen beneath the swollen right kidney. Unfortunately a kidney biopsy was not taken.

Soon afterwards, her blood urea began to rise. It was 316 mg/100 ml on 20.8.57. She developed a generalized vesicular rash and evidence of pericarditis. It was at this point that Wegener's granulomatosis was diagnosed.

Prednisolone 10 mg four times a day was given. Within twenty-four hours her temperature was normal. Over the next few days the shadowing in her lungs became less marked. There was, however, no improvement in her kidneys. She became more uræmic and died on 16.9.57. At autopsy the diagnosis was confirmed and lesions were demonstrated in every organ.

Steroids are of obvious value in the treatment of granulomata of the Wegener type. There was no improvement in the glomerulitis in Case 5. Whether Case 4 had glomerulitis is doubtful, although he did show evidence of some kidney dysfunction in the appearance of red cells and protein in the urine. This is, however, not unexpected in a patient with a high fever.

Reticulosarcoma of the Nasal Passages

This subject has been introduced on account of the difficulty in differentiating, clinically and histologically, between granulomata of the Stewart type and neoplastic disease in the same region which excites the production of granulation tissue.

Case 6

Female, aged 56

In October 1956 she was seen with proptosis of the left eye, which was thought to be due to an ethmoid neoplasm. At operation the left ethmoid labyrinth and frontal sinus were found to be full of soft pale tissue. The histology suggested malignant granuloma (two pathologists arrived at this diagnosis). She was given six treatments of 100 r each in eighteen days. The tumour subsided and in December 1956 there was no proptosis. The swelling recurred in February 1957. A further biopsy suggested that there was a reticulum cell sarcoma present. Professor Symmers' comment on the sections was that the appearances were quite unlike the usual forms of these tumours seen elsewhere in the lymphoreticular system.

Case 7

Female, aged 66

Seen in November 1961 with a large necrotic ulcer on the upper surface of the soft palate and much crusting in both nasal fossæ. Beneath these crusts the mucosa was granular and bled at the lightest touch. She had had a watery rhinorrhœa for two years which had become blood stained latterly.

Sections of tissue taken from the palate and turbinates showed non-specific granulations with much necrosis and angiitis in keeping with a diagnosis of malignant granuloma.

It was decided to give steroids because she had a high ESR (40 mm in 1 hour, Westergren) and a raised serum globulin. Marked improvement followed and after one month the prednisolone was reduced from 60 mg per day to a maintenance dose of 5 mg per day.

She was symptom free in February 1962 but we sought histological proof. Biopsies from the palate and turbinates were taken. The palatal ulcer had healed (Fig 5) but there was still some necrosis present in the left inferior turbinate. The dose of prednisolone was increased to 45 mg per day. In spite of this her disease flared up. A fistula appeared in the left side of the nose beneath the left eye. Multiple shadows appeared in both lungs (Fig 6) and she died on 9.5.62.

Autopsy showed extensive necrosis in the nasal cavities, lungs, kidney, spleen and liver. Histology showed that scattered through these areas of necrosis were sheets of neoplastic reticulum cells.

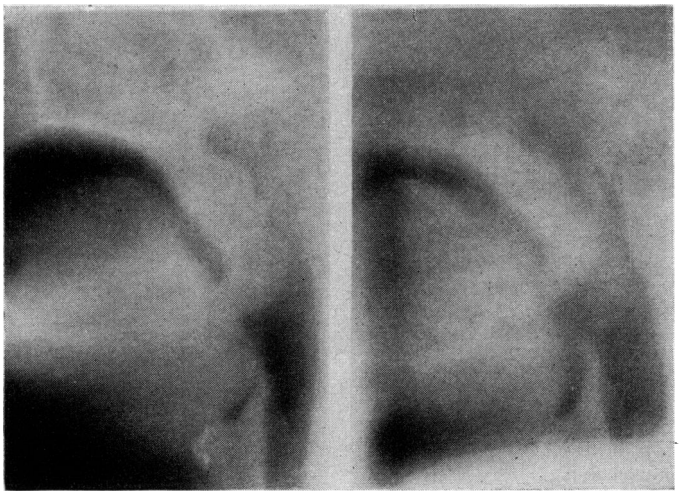

Fig 5 Case 7 *Tomograms of palate showing thickness of soft tissue before (left, 12.1.62) and after (right, 2.4.62) steroids*

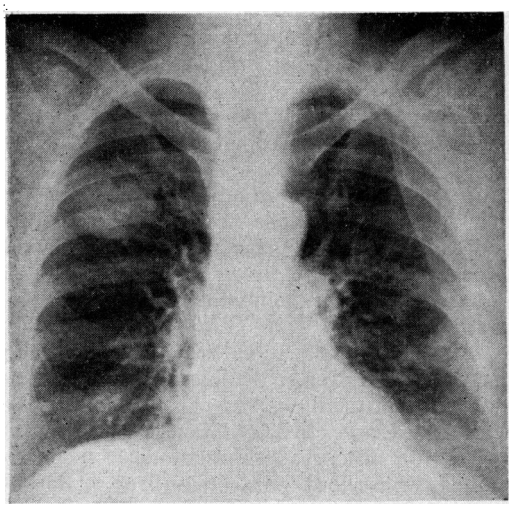

Fig 6 Case 7 *Secondary deposits of reticulum sarcoma in lungs (4.5.62)*

Discussion

Prior to 1955 there were few patients who had survived for more than a few months once the diagnosis of malignant granuloma had been established; interest has been aroused and more successes have been reported since (Ellis 1957, Glass 1955, Howells 1955).

The cases in this series do not illustrate anything new. They tend to support views already expressed that, whether or not the Stewart type and the Wegener type of granuloma have the same hypersensitive basis, the treatment of the two varieties of granuloma is different.

The literature supports the view that low-dosage radiotherapy is the treatment of choice for the classical midline disease (Dixon 1960); the advantage of the low dose is that it may be repeated if necessary; if, however, large fields are used, repeated dosage may be unnecessary. The exact mode of action of radiotherapy is not known; it may be that it destroys the reactive cells in the tissues (Wildermuth 1962) but this is unlikely in the low dose which is effective. Another view is that the irradiation increases the blood supply to the area; the reactive hyperæmia is only transient and one would expect the disease to resume its remorseless progress when the reaction had subsided. Be that as it may, Case 3 has been given vasodilator drugs (nicotinic acid) in the hope that higher local levels of steroid will be obtained.

The use of steroids in a disease with a hypersensitive basis is logical as it is established that antibody production is restrained. It is disappointing that the steroids have little effect on the nose when there is much necrosis present and on the kidney in Wegener's granulomatosis. Hagens (1962) reports a ten-year success using ACTH for nasal ulceration. The glomerulitis appears irreversible, perhaps due to the vascular thrombosis preventing the steroids reaching the affected part. It might be for the same reason that steroids are ineffective in the nose when there is extensive necrosis. Might it not be worth trying the effect of irradiation on the kidneys?

Having decided on the diagnosis and brought the disease under control with the appropriate therapy, two problems emerge.

A facial deformity is not uncommon and repair may be contemplated. Surgery is known to provoke an exacerbation of quiescent disease (Blatt *et al.* 1959) and prostheses are recommended.

If patients have been on steroid therapy a decision when to stop must be made. Case 4 was taken off treatment after his ESR had been normal for one month. Some physicians (Plummer 1963, personal communication) advise a small maintenance dose. If the patient is to be kept on a maintenance dose of steroids close observation for the possible awakening of a dormant focus of tuberculosis is necessary. It is recommended that any patients with evidence of past tuberculosis should be given anti-tuberculous therapy for as long as they are on steroids.

Acknowledgments: I am grateful to Mr Henry Sharp, Mr Lionel Taylor, Dr E C Warner and Dr N S Plummer for their assistance in preparing this paper; also to Miss P Turnbull and other members of the Photographic Department, Charing Cross Hospital, for preparing the illustrations.

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Mr J P Stewart (*Edinburgh*) said that he could not see the rationale for the use of the corticosteroids in midline granulomata as these agents delayed healing and in this condition the process was a progressive and destructive one. He did, however, agree on their usefulness in Wegener's type of this disease where the delicate metastases in the lungs and kidneys were liquidated by its action (cf. breaking down the scar tissue of healed gastric ulcer, &c.).

Mr Harold Ludman (*London*) said that the controversy about classification was of no value unless it enabled predictions to be made about clinical course and response to treatment. Questions that needed to be answered were: (1) Could each case be fitted into one of the two extreme patterns recognized, the Stewart form or Wegener's granulomatosis? (2) What were the minimal criteria that should be applied to make this distinction? There was reason to believe in an immune basis for these diseases. Was it possible to explain the differences between midline granuloma and Wegener's on the magnitude of the immune response, which might affect the local tissue resistance, and the liability to develop generalized hypersensitivity vascular disease?

There was something strange about the favourable response of some cases to X-rays, which were destructive and caused vascular obstruction. Could the granuloma be a basic tissue response, of an immune type, to differing pathological stimuli, which in some cases might be tumours? Could it also be that in these instances the granuloma dominated the clinical and histological picture of the tumour, thereby accounting for those instances in which a tumour had been mistaken for granuloma and also for the response of some granulomata to X-rays?

This idea had been suggested by the case of a 32-year-old man whose clinical course, until death within a few months, had strongly suggested a diagnosis of midline granuloma of the Stewart type. In this case biopsy material, in life, had shown the histological changes of granuloma on several occasions, but post-mortem material, examined at King's College Hospital and later by Professor Friedmann, had shown the true diagnosis to be lymphosarcoma.

Professor I Friedmann in reply said that some of the interesting questions raised by Mr Ludman had already been touched upon in his paper. Others could only be answered on the basis of a systematic study of the immunological problems, as suggested.

As regards classification, Professor Friedmann had drawn attention to the 'blurred margins' that make the histopathological classification of the presenting lesion often so difficult. Figs 5 and 6 (p 293), for instance, illustrated one of the cases studied, whose local nasal lesion was mainly of the histiocytic type, but who died of 'Wegener's granulomatosis' affecting lungs, kidneys and spleen. He agreed that there were instances in which a malignant neoplasm such as a carcinoma or sarcoma was concealed under dense layers of inflammatory granulation tissue. Such a combination, familiar to pathologists, was not confined to the diagnostic difficulties of non-healing granuloma of the nose. Some cases might only be classified when the post-mortem findings were at hand. In some instances of lymphoreticulosarcoma, one might perhaps wonder whether the presenting histiocytic lesion in the nose might be the precursor of these neoplasms. One talked of precancerous lesions, but could one suggest a 'presarcomatous' lesion?

Meeting November 1 1963

Mr J C Hogg (*St Bartholomew's Hospital, London*) delivered his Presidential Address which was entitled **Training Trends in Otolaryngology.**