negative. Results of liver function tests were normal. There was no radiological evidence of oesophageal varices or of gastro-duodenal disease.

Study of the patient's haemoglobin revealed 3.1% alkali-resistant pigment (Hb-F). On electrophoresis an increase in Hb-A_2 was noted in the unstained paper strip (reproduced herewith). On staining with a protein dye and subsequent elution, colorimetry showed the proportion of Hb-A_2 to be significantly raised to 5.1% of the total Hb-A.

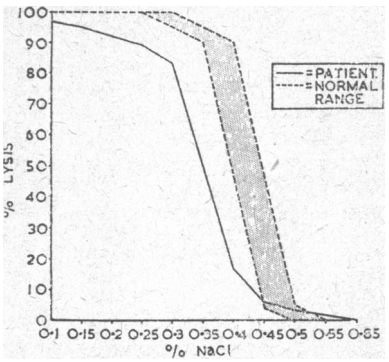
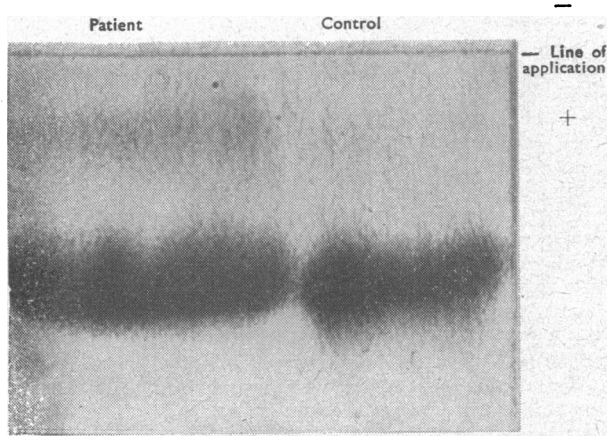


Chart showing osmotic resistance of red blood cells.

The abnormalities demonstrated in this patient's blood may be summarized as an iron-resistant hypochromic microcytic anaemia with target cells, basophilic stippling, and reticulocytosis; increased osmotic resistance of the red blood cells; the presence of Hb-F and an increase in the Hb-A_2 fraction; and a normal level of serum iron. These results provided evidence that the patient had thalassaemia minor, and the diagnosis was conclusively established by the demonstration of similar changes in the blood of two out of three siblings, neither of whom had any symptoms or was conscious of being anaemic (see Special Plate). The patient's only son was normal and thus afforded proof of her heterozygous state (see Table).



Paper electrophoresis of haemoglobin of patient and of a normal control. The strip has not been stained, but even so a band of haemoglobin is visible in the position of Hb-A_2 in the case of the patient but not in that of the control.

Discussion

Reports of thalassaemia in persons of English descent are few. An example was recorded by Bywaters as long ago as 1938. The patient died during the war, but, by the courtesy of Professor Bywaters, we have been in touch with her parents and the blood of neither has the features of thalassaemia. It seems unlikely, therefore, that the case would have met present-day diagnostic requirements. Thalassaemia was noted in a family of Scottish immigrants in Canada (Israels, Suderman, and Hoogstraten, 1955), but there was evidence of illegitimacy in one of the propositus children, and, as they came from a Scottish port, it is probable that the gene was of recent and irregular acquisition. Israëls and Turner (1955) have reported "target-cell anaemia" in two young Englishwomen without Mediterranean ancestry. In both cases the essential criteria required for the diagnosis of thalassaemia were present, and family studies provided supporting evidence.

It seems probable that this disorder is less rare in persons of English stock than these scanty reports would suggest. The discovery of another affected family underlines the importance of considering the possibility of thalassaemia when confronted by a patient with refractory hypochromic anaemia.

Summary

The case is reported of a middle-aged woman of East Anglian farming stock in whom a refractory hypochromic anaemia was shown to be due to thalassaemia minor. Evidence of this disorder was also found in her two brothers, but not in her sister or her son.

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OIL GRANULOMA OF THE LUNG

REPORT OF THREE CASES

BY

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[WITH SPECIAL PLATE]

The condition of lipoid granuloma of the lung was first described in 1925 by Laughlen. The large numbers of reports in the American literature on the subject have recently been reviewed by Buechner and Strug (1956) and also by Steinberg and Finby (1956). Most of the cases reported have been due to collections of liquid paraffin in patients taking this substance by mouth or as nasal drops or sprays. However, mineral oils are not the only source of the trouble, vegetable and animal oils and various fats having also been indicted. In addition there is a special group of cases due to poppy-seed oil used for bronchography.

These exogenous oil and fat granulomas must be distinguished from lesions containing endogenous fatty substances occurring in association with bronchial obstruction and generalized disturbances of fat metabolism. In this paper are reported three cases of lipoid granuloma believed to be of exogenous origin and forming localized tumour masses clinically resembling carcinoma of the bronchus.

Incidence

From the few reports of such granulomas which have appeared in the literature in this country (Paterson, 1938; Rewell, 1947; Belcher, 1949; Nelson, 1954) it might be concluded that the condition is a great rarity, but the three cases here described occurred in the author's practice in just over one year, suggesting that the condition must be fairly common. The cases reported in the literature show that, though the disease may occur at any age, it is fairly common in babies with feeding disturbances, when milk may reach the lungs, where its fat content tends to remain, as it is much more slowly removed than the other constituents. At the other extreme of life it becomes more common again, so that in a hospital treating the aged with such conditions as neurological disorders (especially Parkinsonism), cerebrovascular conditions, and rheumatoid arthritis it has been reported in as many as 14.6% of inmates (Volk *et al.*, 1951). This high incidence is presumably associated with disturbance of swallowing; the

condition has been reported many times in association with achalasia of the cardia (Belcher, 1949; Steinberg and Finby, 1956).

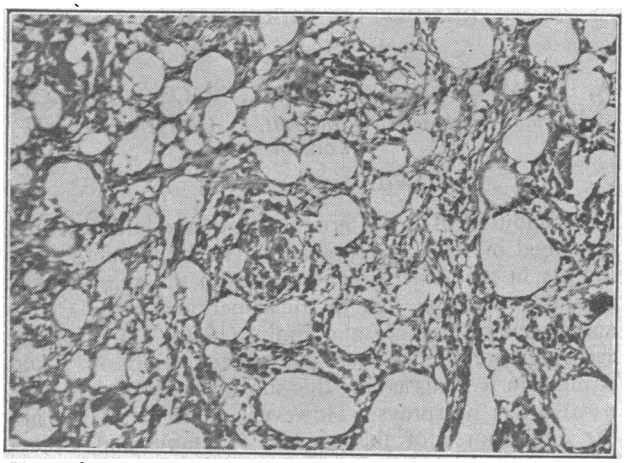
Diagnosis

The symptoms are often minimal, though some cough and breathlessness are common and occasionally there is haemoptysis. These patients, however, often develop lung infections in association with the oil granuloma, and it is in this way that most of such cases come to light.

The recognition of oil granuloma may avoid an unnecessary operation, though even at operation the diagnosis from carcinoma may be very difficult, but if made will allow of a less extensive resection than that designed for malignant disease.

Case 1

A man aged 72 reported sick because of recent cough with some dyspnoea. He was a heavy pipe smoker. Examination revealed abnormal signs at the base of the left lung, but no finger-clubbing and no other significant disease. Radiography (Special Plate, Fig. 1) showed a lesion in the postero-basic segment of the left lower lobe. No abnormality was seen bronchoscopically. At operation an exceptionally hard "cobblestone" mass was felt in the lower lobe and the lobe was removed. The specimen contained a firm, fairly well demarcated greyish mass measuring 5.5 by 4 by 2.5 cm. in the lateral basal segment. The bronchi were normal. Microscopical examination showed a mesh of dense fibrous tissue containing numerous large vacuoles of lipoid material; the histological appearance is shown in the accompanying photomicrograph. A foreign-body giant-cell reaction was present in some areas, and there were similar changes in the hilar lymph nodes.



Photomicrograph (×50) of section of left lower lobe, showing dense fibrous tissue containing large vacuoles of lipoid material (Case 1).

Subsequent questioning elicited that the patient habitually took liquid paraffin as an aperient. He made an uneventful recovery, and during the eighteen months since operation he has had no further chest symptoms, though he has aged considerably, becoming partly senile.

Case 2

A woman aged 56. *X*-ray examination one month before operation showed a mass confined to the right middle lobe. She was almost symptom-free, though she had a dry cough which she attributed to smoking. In the course of the month's observation she had a pyrexial illness, which was treated with penicillin. No abnormality was seen on bronchoscopy. At operation a hard, rounded lesion about 1½ in. (3.75 cm.) in diameter was found. Examination of a frozen section confirmed the diagnosis. The middle lobe only was removed. The specimen contained a clearly defined, very firm greyish mass measuring 3.6 by 2.4 by 2.2 cm. The bronchi were normal. Microscopical examination showed a dense fibrous-tissue meshwork enclosing large droplets of lipoid material, a few small areas of active inflammation with giant-cell reaction were present.

The post-operative course and the six months since operation have been uneventful. The patient denies having taken liquid paraffin by mouth or using nasal drops or sprays at any time.

Case 3

A man aged 41, who gave a history of polyneuritis for six years. For the first two of these he was in hospital and suffered from dysphagia; he also had two attacks of pulmonary infection followed by breathlessness. A year before the lung condition was found his dysphagia was shown to be due to achalasia of the cardia; a myotomy of the cardia (Heller's operation) was performed, completely relieving the dysphagia. However, a barium-meal examination two months after the operation showed some retention in the oesophagus 20 minutes after swallowing; the contour of the oesophagus appeared normal.

The first chest radiograph was taken one month before his admission, and revealed a mass in the right upper and middle lobes, which had enlarged considerably by the time he reached hospital (Special Plate, Figs. 2a and b). He then had a slight productive cough and was breathless on exertion. His sputum was not examined for fat, and bronchoscopy revealed no abnormality. The large-sized shadow in association with a normal bronchoscopic appearance led to discussion of lipoid granuloma as a possible diagnosis, for had there been a carcinoma one would have expected to see a lesion with the bronchoscope. At operation a large, hard, lobulated tumour mass was seen in the right upper lobe with a fingerlike process extending into the middle lobe. Frozen section at operation established the diagnosis of lipoid granuloma, though even this did not exclude the possibility of a small carcinoma within the mass. The right upper lobe only was removed. The specimen contained a well-defined, firm area, 10 by 6 by 4.5 cm., in the posterior segment, the mass consisting of grey, semitranslucent tissue. The bronchi appeared normal. Microscopical examination showed the presence of very numerous droplets of lipoid material. In some areas there was an intense, acute inflammatory reaction with numerous giant cells around the lipoid, in others the lipoid material was surrounded by dense fibrous tissue. There were similar changes in the mediastinal lymph nodes.

The post-operative course was complicated by a bronchopleural fistula with an apical air-space, which did not become infected. Two months after operation a four-rib thoracoplasty was performed to close the persistent pleural space, and within a few weeks this appeared to be completely obliterated. Later a localized shadow was visible in the apex of the left lower lobe, and twelve months after operation this shadow had become much larger. It is presumed that the shadow represents a new area of lipoid granuloma in the lower lobe. The patient remains symptom-free except for a minimal dry cough. Questioning after the diagnosis was suspected reveals no history of the use of liquid paraffin.

Discussion

In Case 1 a history of the use of liquid paraffin over many years fits in with the final diagnosis, though there was no disturbance of swallowing. In Case 2 no such history was obtained even on cross-examination after the diagnosis was established. No doubt oil or fat capable of producing the lesion was included in the diet, but once again there was no explanation of why it reached the lungs. In Case 3 the history of achalasia of the cardia is characteristic, and, though no oily medicaments were taken, the inhalation of food from the abnormal oesophagus can be presumed, for it has been shown to be a common event in such cases. Owing to the absence of lung symptoms a radiograph was not taken until some months after the Heller operation. The features which are more difficult to explain are the increase in size of the lung shadow over the months following the operative relief of the achalasia, and its recurrence after removal of the upper lobe, when only a minimal lesion was

palpable in the middle lobe. One is forced to the conclusion that the 20-minute delay in emptying the oesophagus seen after the barium meal is significant, and that during sleep some of the oesophageal contents spilt over into the lung, it being well known that in patients with achalasia an advanced degree of food retention in the oesophagus may occur without their noticing it.

The clinical and *x*-ray findings in these three cases suggested a carcinoma, but in each of them one would have expected the carcinoma to be visible at bronchoscopy. Indeed, after the experience of the first case the negative bronchoscopic findings led to doubt of this diagnosis, and the exceptionally hard and lobulated feel of the mass at operation helped to confirm the suspicion that the lesions were oil granulomas. At two of the operations it was possible to obtain further evidence by frozen sections of a biopsy taken from the lesion.

The presence of fatty globules in the sputum, as was found in one of these cases, is strong evidence of oil granuloma and is undoubtedly the most helpful pointer to the diagnosis. Radiologists have described the *x*-ray appearances of these lesions in great detail, and may be able to suggest the diagnosis when the lesions are multiple and occur in the "aspiration" areas of the lungs, but there are no radiological features which allow certain distinction from carcinoma or the "pneumonias." There are many oily substances which may reach the lungs and give rise to this granulomatous condition, varying from the very inert mineral oils (for example, hydrocarbons such as liquid paraffin) to partially unsaturated vegetable and animal oils and fats (cod-liver oil, butter fat, etc.) (Kaplan, 1941). Staining with the fat stains in common use in histology and examination with polarized light (Wagner *et al.*, 1955) may go some way towards the identification of the substance, but there are many difficulties in analysing the small quantities of substance available, and it is fortunate that such exact analysis is rarely necessary.

The histology described in the case reports is typical of the condition. It has been suggested that the acute reaction is more pronounced when the foreign material contains unsaturated fats. In all cases of long standing fibrosis dominates the picture, but many oily globules remain enmeshed in the fibrous tissue (Pinkerton, 1928; Ikeda, 1937).

Summary

Three cases of oil granuloma of the lung are described. Each simulated, both clinically and radiologically, a bronchial carcinoma and was treated by resection. The condition usually results from taking liquid paraffin by mouth or in nasal sprays and is often associated with disturbances of swallowing; thus it is seen in infants with feeding difficulties and in adults with neurological disorders and diseases of the oesophagus. Once it has been suspected it may be diagnosed by finding fatty globules in the sputum.

In one of the cases reported liquid paraffin had been taken for many years. Another patient had achalasia of the cardia, which had been treated surgically. In the third case there was no explanation of the origin of the granuloma. One of the cases was most unusual in that the lung lesion appeared to be progressive after removal of the grossly affected lobe.

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SOME CLINICAL APPLICATIONS OF VAGINAL SMEARS IN GYNAECOLOGICAL ENDOCRINOLOGY

BY

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[WITH SPECIAL PLATE]

The use of the vaginal smear as a method for studying ovarian function is based on the fact that the structure of the vaginal epithelium, like that of the endometrium, is specifically influenced by the ovarian hormones. In 1847 Pouchet published his classic book in which he described the cellular picture of vaginal fluid and its changes during the human menstrual cycle. This work appears to have been forgotten, although in the late nineteenth and early twentieth century several investigators were using the vaginal-smear technique in animal experiments (Lataste, 1893; Stockard and Papanicolaou, 1917; Allen and Doisy, 1923). Later it was again applied to the study of the human menstrual cycle (Papanicolaou, 1933), but it was not until 1936 that Papanicolaou and Shorr recognized its value in relation to the sex hormones.

Since 1943 the clinical application of vaginal cytology has been well established in North and South America by Papanicolaou and Traut (1943), Shorr (1945), and De Allende and Orías (1950). In Belgium Pundel (1950, 1952) and Pundel and Van Meensel (1951) published their very extensive studies on this subject, including the value of vaginal cytology in pregnancy, and more recently we are informed that in Denmark and Sweden the vaginal-smear technique has become a routine procedure in the leading gynaecological endocrine units, though it is still rarely used in this country except for the diagnosis of cancer.

Present Study

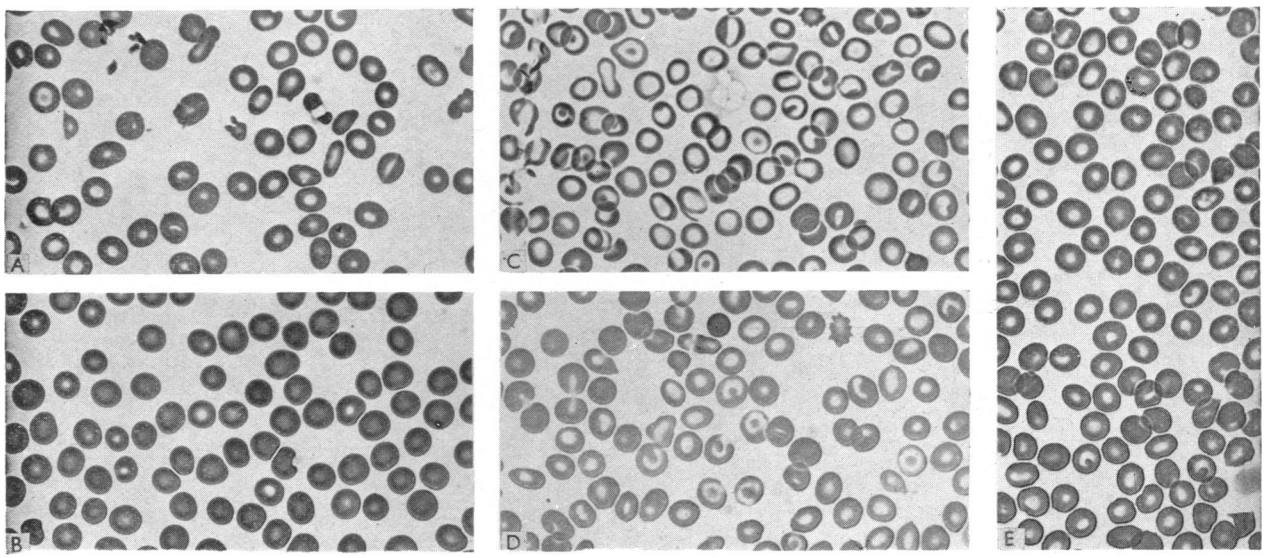
From our preliminary work in the Endocrine Department at Chelsea Hospital for Women, where one of us (M. M.) is investigating the possible relationship between oestrogen and uterine carcinoma, we believe that vaginal cytology in experienced hands can be of value in assessing ovarian function. In many patients it is advisable to study daily smears over a period of four to six weeks, and we have found that the majority of patients after instruction are able to take their own smears satisfactorily.

Our observations are based on vaginal smears taken from 110 patients who were attending Dr. P. M. F. Bishop's endocrine clinic and 40 patients attending Mr. J. B. Blaikley's cancer follow-up clinic at the Chelsea Hospital for Women. In the latter case only single smears were taken, while from the others either periodic or daily smears were obtained.

Method of Taking and Examining Smears

The vaginal smear is obtained by aspirating the secretion from the posterior fornix of the vagina. For this purpose we use a "pyrex" glass tube of 5 mm. internal diameter and approximately 6 in. (15 cm.) in length; one end is

C. W. H. HAVARD *ET AL.*: THALASSAEMIA MINOR



Appearance of red cells of patient (A), her son (B), her two thalassaemic brothers (C and D), and her normal sister (E). (×500)

A. H. M. SIDDONS: OIL GRANULOMA OF LUNG

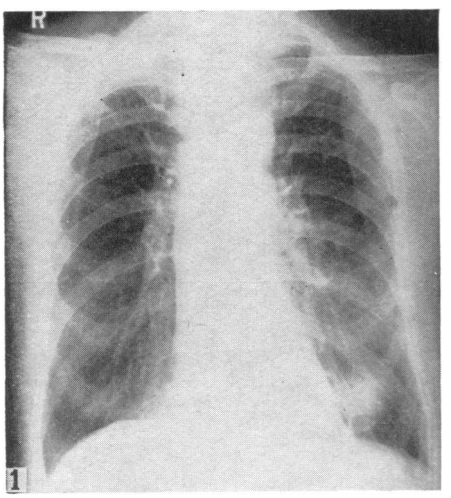


FIG. 1.—Case 1. Radiograph showing lesion in postero-basic segment of left lower lobe.

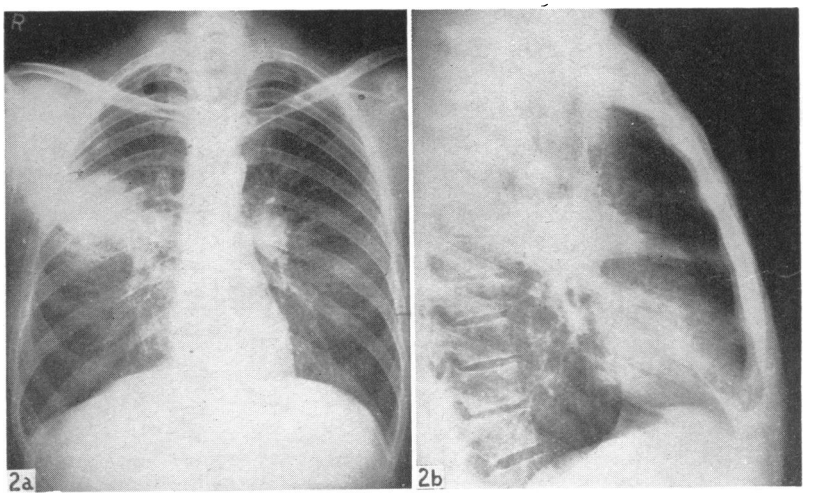


FIG. 2*a*, *b*.—Case 3. Radiographs showing mass in right upper and middle lobes.

F. OSMOND-CLARKE AND M. MURRAY: VAGINAL SMEARS

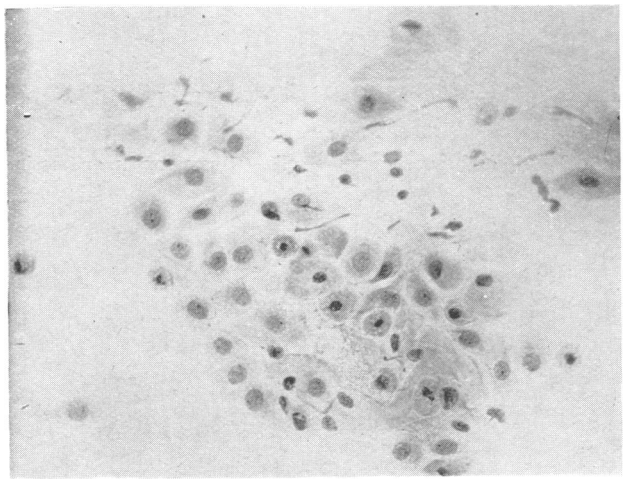


FIG. 1.—Vaginal smear from patient with secondary amenorrhoea, showing marked degree of atrophy of epithelium. (×240.)

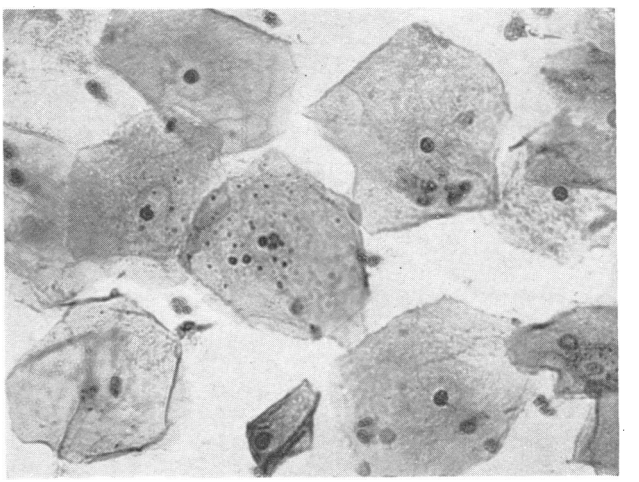


FIG. 2.—Vaginal smear from patient with ovarian agenesis, showing marked oestrogenic activity six months after implantation of 300 mg. stilboestrol. (×240.)