SIMULATION OF CANCER BY OIL GRANULOMAS OF THERAPEUTIC ORIGIN

BY

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This is the record of six patients, each of whom presented a tumour-like oil granuloma* which was mistaken for cancer. In every case the lesion had resulted from the introduction of some oily substance into the tissues during treatment of an earlier disease. In three of the cases the possible diagnostic significance of the history of this treatment was not appreciated until after microscopy had shown the real nature of the granuloma; in the other three cases not even the history of the previous illness had been elicited. Four of the patients were subjected to unnecessarily radical treatment because of the incorrect clinical diagnosis of cancer. Two patients were less unfortunate, for histological examination while the operation was in progress showed that the lesion was not neoplastic; the surgeon was therefore able to deal with it by local excision instead of having to carry out the radical procedure for which the patient had been prepared.

These six cases have been chosen from 14 similar examples which I have seen during the last ten years. Most of the cases were referred to me by colleagues—surgeons and pathologists—whom I am glad to thank for notes of patients' histories and for specimens. The cases are from different parts of Britain and from abroad; they do not represent the material of any particular centres.

Case 1

Anal oleogranuloma following injections for haemorrhoids: abdomino-perineal excision of rectum.

A middle-aged business man found difficulty in passing faeces while on a fortnight's holiday. It seemed to him as if the faeces, which had become harder than usual, were held up by failure of the anal passage to open sufficiently. Soon after his return home his motions regained their usual consistency and the symptom disappeared: it did not recur. He mentioned his experience to a doctor soon afterwards, and examination showed a hard, rather nodular constriction of the upper part of the anal canal. The constriction was presumed to be an annular carcinoma, and abdomino-perineal excision of the rectum and anus was performed without preliminary biopsy. Histological examination of the specimen showed that the lesion was a sclerotic oleogranuloma; there was no evidence of neoplasia. It was then learnt that haemorrhoids had been treated by about 20 injections of phenol in almond oil during the three years before excision of the rectum.

Case 2

Ischio-rectal oleogranuloma after packing of abscess cavity with paraffinized gauze: abdomino-perineal excision of rectum.

A young man developed an acute abscess in the left ischio-rectal fossa. The abscess was incised, and its cavity was packed with gauze tape; the gauze had been smeared with yellow soft paraffin in order to make its withdrawal easier. During the following week the packing was extracted, a few inches at a time, until by the eighth day its removal was complete. A month later there was still a small discharging sinus at the site of the incision, and a firm, painless mass in the left ischio-rectal region was felt through the wall of the rectum. The mass was presumed to be a carcinoma which had broken into the ischio-rectal fossa from a clinically inapparent primary growth in the rectum. The fossa was explored surgically and the findings were thought to confirm this diagnosis; abdomino-perineal excision of the rectum and ischio-rectal tissues was per-Microscopy showed that the ischio-rectal mass was a typical oleogranuloma; the rectum was normal. The patient became increasingly depressed by having a permanent colostomy and by the unrelieved fear that the operation might not have cured the "cancer." He was sent abroad for a rest, and died there, a few months later, from an accidental overdose of sleeping draught. No evidence of malignant disease was found at necropsy.

Case 3†

Oleogranuloma of breast following packing of abscess cavity with medicated paraffin paste: radical mastectomy.

A young woman accidentally pierced the skin of the lower outer quadrant of her right breast with a needle which had just been used for aspirating pus from a patient's subperiosteal abscess. She developed an acute breast abscess, from which 10 ml. of pus was evacuated through a stab incision, 0.5 cm. long. The abscess cavity was filled with a paste of bismuth, iodoform, and liquid paraffin; a firm, occlusive dressing was applied. No other treatment was given. Staphylococcus aureus was isolated from the pus. After a week, when the dressing was removed, the incision had healed over; the underlying tissues were indurated.

Two months later a slightly tender nodular mass, about 2 cm. in diameter, was found at the site of the abscess; it was fixed to the skin and to the pectoral muscle. The mass slowly enlarged; within another month peau d'orange and dimpling had appeared over it, and a group of lymph nodes had become palpable under the anterior axillary fold: the nodes were neither painful nor tender. The condition was thought to be a chronic staphylococcal granuloma; attempts to aspirate it were unsuccessful, and a wedge resection of the affected part of the breast was carried out. The mass was bisected by the surgeon immediately after excision: it was solid and hard, and speckled with small yellow spots from which thick cream-like material oozed when the tissue was squeezed; scirrhous comedo cancer was diagnosed macroscopically, and radical mastectomy was performed without further ado. Microscopical examination showed that the condition was a typical sclerosing oleogranuloma, with focal oleogranulomatous lymphangitis and lymphadenitis. There was no evidence of neoplastic disease. The creamy material was shown to contain liquid paraffin and bismuth.

Case 4

Scrotal oleogranuloma following injection of a hydrocele sac: bilateral orchidectomy.

A young man was discomforted by the presence of a varicocele and a small hydrocele of the tunica vaginalis,

^{*&}quot;Oil granuloma" ("oleogranuloma") should be distinguished from "lipogranuloma." Lipogranuloma results from some alteration in the patient's body fat—for example, in traumatic fat necrosis—whereas the granulomatogenic material in oleogranuloma is an oily substance foreign to the patient's tissues.

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"Oil" is used in this paper as a name for a range of substances wider than is understood in the strict chemical use of the word, and including true oils, liquid and solid paraffins, and waxes. As the reaction of the tissues is essentially the same whether the granulomatogenic "oil" is liquid or solid, granulomas due to the presence of the solid paraffins and waxes are included here under the term oil granuloma or oleogranuloma; the word "paraffinoma" is avoided.

[†]This case is recorded at the request of the patient and of her husband, who performed the mastectomy.

both on the left side. The varicocele was successfully treated by three watery injections of sodium morrhuate. The hydrocele increased in size more rapidly after the varicocele had been treated; it was aspirated on several occasions but always rapidly refilled. With the intention of obliterating the sac an injection of 2 ml. of niaoul oil (the essential oil from *Melaleuca viridiflora*), 20% in liquid paraffin, was made through the aspirating needle after each of five fortnightly aspirations. The injections caused an inflammatory reaction, with rapid accumulation of fluid in the sac; the amount of fluid was less after each injection, and after the fifth injection the hydrocele was regarded as cured.

Six months later the patient reported a recurrence of swelling in the scrotum. Examination showed a hard, nodular, painless mass, about 5 cm. in diameter, which occupied most of the left half of the scrotum, apparently replacing the testicle on that side and adherent to the other testicle and to the skin. Small ill-defined nodules were palpable in the lower part of the left spermatic cord. The Wassermann and Kahn reactions were negative. diagnosis of malignant testicular neoplasm was made; the scrotum was removed with its contents and the spermatic cords, and a bilateral block dissection of the inguinal and femoral lymph nodes was carried out. Macroscopical examination of the specimen showed that the tunica vaginalis on the left side was obliterated, the testicle being covered in front and on both sides by an ill-defined nodular mass of densely fibrous tissue which in places extended into the dermis and across the midline to the opposite tunica vaginalis; nodules of similar tissue were present in the left spermatic cord. Microscopically, the tumour-like tissue was a sclerosing oleogranuloma; the left testis and epididymis and the vas deferens were unaffected by the surrounding granulomatous process and appeared to be histologically normal. The right testis, epididymis, and vas deferens were macroscopically and microscopically normal. The inguinal and femoral lymph nodes showed only the mild non-specific inflammatory changes which are commonly seen in the nodes in this region. No evidence of neoplasia was found in any of the tissues.

Comment

In the four cases which have been described the failure to recognize the granulomatous nature of the tumour-like lesions was disastrous. In none of them was biopsy performed, nor were frozen sections examined during the operation. Whether the therapeutic procedures which resulted in development of the granulomas were well advised would be more competently discussed elsewhere; there is no doubt, however, that in each case the history of the treatment should have suggested the possibility of a granulomatous process, so indicating the special need for histological examination before deciding on the extent of the operation.

In the following cases the oleogranulomatous nature of the lesions was demonstrated histologically during the operation: radical surgery was therefore avoided.

Case 5

Simulation of sarcoma by an intramuscular oleogranuloma following injections of an oily suspension of bismuth.

A woman aged 26 complained of discomfort in the right buttock when riding side-saddle on horseback. It felt to her as if a pebble rolled between the muscles as they moved. Examination showed an irregular mass, apparently within the gluteus maximus. Radiographs were reported upon as showing several irregular shadows in the gluteal musculature on the right side, suggesting the presence of bismuth or similar injected material. The patient said that she had never had any injections: it was therefore thought that the lesion was probably a partly calcified neoplasm. She was told that the likeliest diagnosis was sarcoma and that a hind-quarter amputation might be necessary if this diagnosis was confirmed on exploration of the buttock.

At operation a dense mass of tissue, macroscopically resembling fibrosarcoma, was found in the gluteal musculature. A frozen section showed only oleogranulomatous tissue, and surg cal treatment was therefore limited to local removal of the mass by sharp dissection. Exhaustive histological examination of the excised tissue confirmed that the lesion was a sclerosing oleogranuloma; there was no evidence of neoplasia. Bismuth was readily demonstrated in the tissue. The patient eventually admitted that 18 months earlier she had completed treatment for syphilis which had been diagnosed in the secondary stage. This treatment had consisted of alternating courses of oxophenarsine hydrochloride B.P. 1953 intravenously and of intramuscular injections of a suspension of bismuth metal in a creocamph base (this base contained camphor, creosote, Japan wax, and palm butter). She had had about 50 intramuscular injections, almost all of them into the right buttock. There was no clinical or serological evidence of syphilis when she was examined during convalescence from the operation; the cerebrospinal fluid was normal.

Case 6

Simulation of sarcoma by an intramuscular pseudotuberculous oleogranuloma following injections of penicillin with beeswax in oil.

A middle-aged woman noticed a painless lump in one thigh while washing. The lump slowly got bigger during the next ten weeks. A surgeon advised admission to hospital for biopsy, followed by amputation if the clinical diagnosis of sarcoma was confirmed. Accordingly, an incision was made over the lesion, which presented as a vascular, yellowish mass, apparently infiltrating the vastus lateralis: a frozen section of a piece of the mass was examined immediately and showed oleogranulomatous foci and conspicuous tubercle-like structures. The rest of the lesion was dissected out from the muscle. Examination of the whole specimen confirmed the findings in the frozen section; most of the tubercle-like structures were characteristic sarcoid lesions, although some had formed around the typical macrophage-lined oil-containing lacunae of an oleogranulomatous lesion. No isotropic or anisotropic foreign bodies were found in ordinary sections or in thick sections (40 micra), and no micro-organisms were seen. The recognition of tuberculoid tissue in the original frozen section led to bacteriological investigation of the freshly excised tissue: no organisms were seen in smears; cultures on blood-agar, Sabouraud's medium, and Löwenstein-Jensen medium were sterile; and no disease developed in four guinea-pigs which were killed at intervals of 6, 12, 20, and 32 weeks after inoculation with a suspension of the granulomatous

There was no clinical evidence of sarcoidosis; radiographs of the chest and hands were normal, the plasma proteins and the blood picture were normal, and the Mantoux test (old tuberculin, 1:1,000) was positive. The Wassermann and Kahn reactions were negative. The patient then remembered that she had had several injections of penicillin into the affected thigh as treatment for recurrent furunculosis. Her own doctor confirmed that about 18 months before the lump appeared he had given her a course of 15 weekly injections, each of 1 ml. of a commercial preparation of benzylpenicillin with beeswax in arachis oil; he pointed out that the granuloma had developed in the area which he customarily chose for intramuscular injections. The patient is in good health, without evidence of sarcoidosis, three years after the operation.

Oil Granulomas: Some General Comments

The granuloma in each of these cases was caused by an oily foreign substance which had been introduced therapeutically into the tissues. The "oils" concerned were: almond oil, as the vehicle for phenol (Case 1); yellow soft paraffin (Case 2); liquid paraffin as the base of bismuth, iodoform, and paraffin paste (Case 3), and as the diluent

in a preparation of another oil, oil of niaoul (Case 4); a base containing camphor, creosote, Japan wax, and palm butter as the vehicle for bismuth metal (Case 5); and arachis oil and beeswax as the vehicle for penicillin (Case 6). There is no reason to believe that the active ingredients of the preparations used played any part in the causation of the granuloma.

The development of oil granulomas following therapeutic or diagnostic procedures has often been recorded; the relevant literature can readily be traced in reference works, such as the Quarterly Cumulative Index Medicus, and needs no detailed reference here. Some of the grossest examples have been complications of oleoperitoneum (Cruickshank, 1941) and oleothorax (Ballantyne et al., 1952). Inhalational oleopneumonia ("lipopneumonia") is a wellknown misadventure of this sort, and has been known to simulate cancer (Stonehill and Bodon, 1955). At the other extreme are minute focal oleogranulomas, found incidentally -for example, in sections of surgical specimens; Aaron and Levine (1954) described such a lesion in an endometrial biopsy from a patient after hysterosalpingography using iodized oil. Minor degrees of oleogranulomatous reaction are probably very common in the presence of foreign oils, although serious manifestations are rare.

Comparable granulomas may result from accidental entry of oil into the tissues, particularly if a considerable quantity of mineral oil is injected under pressure—for example, "grease-gun hand" (cf. Moore, 1946). Similarly, paraffin wax, injected into the tissues for cosmetic reasons or to alter the features, has been responsible for the development of oleogranulomas ("paraffinomas") (cf. Andrews, 1954), which in the monstrousness of the resulting disfigurement can equal the ravages of leprosy, lupus, and syphilis. Such distortions have also stricken quasi-impotent psychopathic unfortunates who have injected wax into their own tissues (Best et al., 1953).

Oil granulomas which give clinical manifestations may develop quite rapidly after the oil enters the tissues, or they may first appear months or, rarely, even years later. People differ in the intensity and extent of their reaction to the same oil, and oils differ in their granulomatogenic capacity. The site affected, the nature and the amount of oil present, the physical characteristics of the oil, such as emulsification, the availability of enzymes capable of breaking it down, and changes in the tissues, such as scarring, which may interfere with dispersal of foreign material, are factors which may be important in the pathogenesis of oleogranulomas. Vegetable oils are commonly believed to be unlikely to cause a reaction in the tissues, whereas mineral oils are supposed regularly to do so, and animal oils to occupy an intermediate position. The occasional development of oleogranulomatous lesions in the spinal theca after myelography, in the uterine tubes and pelvic peritoneum after salpingography. and in the lungs after bronchography is evidence of the potential harmfulness of vegetable oils (iodized poppy-seed, arachis, or sesame oil); Case 1, above, is apparently another example of the granulomatogenic activity of a usually bland vegetable oil (almond oil), and similar observations are not very rare.

On the other hand, the absence, in some cases, of any apparent reaction around prosthetic implants of hard paraffin indicates that on occasion even the notoriously granulomatogenic paraffins are not necessarily harmful. However, such prostheses are inserted in the form of already moulded solid masses, whereas the paraffins used for cosmetic purposes or disguise are injected in the fluid state at a temperature above that of the body, solidifying as they cool to body temperature. It is obvious that the latter procedure must offer an opportunity for dispersal of minute droplets of the wax while it is still fluid. Small droplets of liquid oils may be carried to lymph nodes, and focal oleogranulomas may develop along the course of the lymphatics and in the nodes themselves, as in Case 3.

Simulation of Cancer by Granulomas

Foreign-body granulomas rarely mimic cancer: when they do, the consequences of failure to recognize their real nature may be disastrous. Oily and siliceous materials seem likelier than other foreign bodies to be the cause of tumour-mimicking granulomas, yet only a few of the granulomas which even they cause are apt to simulate neoplastic disease. Suture materials, usually silk and cotton, are a rare cause of abdominal granulomas which may be misdiagnosed as cancers ("Schloffer's tumours": Roska, 1939). In most cases the history and the site of the lesion indicate the possibility of a foreign-body reaction; biopsy is invaluable in avoiding mistaken diagnosis.

Oil granulomas, as occasional simulants of cancer, have been discussed above.

Siliceous granulomas.—Shattock's (1916-17) pseudotuberculoma silicoticum is a classical example of a siliceous granuloma which on occasion may simulate cancer. Typically, this lesion develops as a delayed result of contamination of superficial wounds by siliceous materials such as gravel, sand, and slate. Its fixation to adjacent structures and its progressive enlargement may suggest a neoplasm clinically, particularly if the history of injury is overlooked -indeed, the injury may have been forgotten, for years may elapse before the granuloma takes on active growth. The granulomatous reaction in these lesions, unlike that in pulmonary silicosis, is of sarcoid type; the significance of this sarcoid reaction to siliceous material has been discussed recently by Refvem (1954). Löfgren et al. (1955) observed that the onset of growth of siliceous granulomas coincided in a considerable proportion of cases with the development of systemic sarcoidosis; this association was a feature of some of the cases which I have seen, although others have developed no manifestations of any generalized disease during a follow-up period of several years. Neoplasia may also be mimicked by post-operative talc granulomas, as in a case reported by Baar (1953), and in two cases of mine.

I have not come upon any record of an oil granuloma which was associated with a sarcoid tissue-reaction: Case 6, in which a characteristic sarcoid type of granulomatous reaction was associated with typical lacunar oleogranulomatous tissue, is the only instance of such a reaction known to me; the patient has shown no evidence of sarcoidosis. Philpott et al. (1954) described a simple sarcoid reaction at the site of injection of "procaine penicillin G suspension," an observation which suggested to them that penicillin itself might occasionally evoke a granulomatous reaction; their conclusions are debatable, and of doubtful relevance to the findings in Case 6.

Infective and Infestive Granulomas.—Infective granulomas such as tuberculomas, gummas, and fungal granulomas, are well known to be able on occasion to simulate neoplasms. Granulomatous masses due to infestation by metazoan parasites may be mistaken clinically for cancer. My father (Symmers, 1903, unpublished observations), working in the laboratory of the Kasr-el-Aini Hospital in Cairo, saw a number of these confusing lesions due to the presence of schistosome ova in unusual situations.

Cancer as a Sequel of Injection of Oil

There does not appear to be any record of cancer developing at the site of an oleogranuloma. The possibility that true neoplasms might result from the presence of foreign oil in the tissues cannot be passed over, in view of the possibility that the oil might contain carcinogenic fractions. Goldenberg (1954) described two cases which he regarded as examples of fibrosarcoma, possibly caused by sesame oil which had been the vehicle for penicillin administered intramuscularly. Oleogranulomatous changes are not mentioned in his account of the cases. While his deductions may be open to argument, his report is a timely reminder of another possible complication of introducing oils into the tissues.

Summary

Six cases in which oil granuloma simulated cancer are described. The oil was introduced into the tissues therapeutically in every case. In four cases biopsy was not undertaken, and the patient underwent unnecessarily radical surgical treatment before the true nature of the lesion was recognized (excision of rectum in two, radical mastectomy in one, and castration in one). Timely histological examination enabled the granulomatous nature of the tumour to be recognized in the other two cases, and radical surgery was avoided.

It is probable that radical treatment would have been avoided in all these cases had the possibility of a granuloma been considered and biopsy performed. A feature common to all the cases was the failure to elicit the history of previous treatment with oily substances, or, when it was known, to recognize its significance.

Other types of tumour-mimicking granulomas are mentioned briefly.

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ANNULAR DETACHMENT OF THE **CERVIX**

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Annular detachment or spontaneous amputation of the cervix is an uncommon complication of pregnancy. The condition was first described by Scott (1821). De Costa (1933) reviewed 16 cases collected from the literature and added a further one. In a later and more extensive review, Ingraham and Taylor (1947) analysed the clinical findings in 55 patients. Since then Arnott (1949), Uhma (1949), and Manly (1949) have each reported a case, and Jeffcoate and Lister (1952), in a paper postulating the probable mechanism and cause of cervical detachment, record the details of labour in an additional four

The following is the case history of a patient who developed this interesting complication during the course of a prolonged labour.

Case Report

A primigravida aged 26 first attended the antenatal clinic when she was 10 weeks pregnant. On physical examination her general condition was good, the heart, lungs, and abdomen were normal, and on vaginal examination the uterus was in good position and corresponded in size to the period of amenorrhoea. The patient was booked for confinement in hospital and was asked to return to the clinic at regular intervals for antenatal supervision.

Pregnancy progressed satisfactorily until the 38th week, when it was found that the greatest diameter of the foetal head was still above the pelvic brim. As abdominal and vaginal examinations failed to detect an obvious cause for the "free" head, x-ray pelvimetry was carried out. The x-ray pictures revealed an android pelvis with measurements adequate to accommodate the foetal head, and a favourable outcome for vaginal delivery was predicted.

At the 41st week the patient was admitted to hospital in early labour. On examination her general condition and morale were good, her blood pressure was 125/75 mm. Hg, and albumin and acetone were not present in a specimen of urine. The foetus presented by the vertex with the back to the right and in front, and although the foetal head had settled in the brim, the greatest diameter had not descended into the pelvis. The foetal heart was regular and the membranes were intact.

Nineteen hours after the onset of labour moderately strong uterine contractions were occurring at intervals of three minutes, the foetal head had descended into the pelvis, and the condition of both mother and foetus was good. The patient's urine contained a marked trace of acetone, therefore a pint (570 ml.) of 20% glucose was administered by intravenous drip, following which the patient was given 1/3 gr. (22 mg.) of "omnopon" and 1/150 gr. (0.43 mg.) of scopolamine as a sedative.

Thirty-one hours after the onset of labour the uterine contractions had diminished in strength and frequency, and, because of the poor progress in labour, vaginal examination under general anaesthesia was carried out. This examination showed the cervix to be dilated three fingerbreadths, thin, and well applied to a tense bag of forewaters; the foetal head, which was well flexed, lay at the level of the ischial spines in the right occipito-transverse position. From these findings it was concluded that the cause of delay was not due to cephalo-pelvic disproportion, and it was decided, therefore, to allow labour to continue.

Fifty-two hours after the onset of labour the quality of the uterine contractions had improved. On rectal examination the cervix was almost half-dilated and the bag of forewaters was still intact. Omnopon and scopolamine were repeated by injection, and for the next 12 hours the patient rested well between her contractions. Re-examination at the end of this period showed that further cervical dilatation had not occurred, but in view of the good condition of the mother and foetus it was decided to repeat the sedative and postpone the question of termination by caesarean section until a further 12 hours had elapsed.

Seventy-four hours after the onset of labour the bag of forewaters ruptured spontaneously. The uterine contractions were moderately strong in character and, although the foetal heart was regular and the liquor free from meconium, the maternal pulse had risen to 110 beats a minute. On rectal examination the cervix was half-dilated and had become thick and oedematous. In the light of these findings it was decided to perform caesarean section.

During the preparation of the patient for operation, she suddenly expressed the desire to "bear down" and within a few minutes the foetal head appeared at the vulva. Normal delivery of a live 7-lb. (3.2-kg.) female child was rapidly followed by separation of the placenta and membranes. On cleansing the vulva at the completion of the third stage, a firm, round reddish-purple tumour was noted at the introitus. The tumour consisted of a thick saucer-shaped rim of cervix. the rim measuring approximately 1 in. (2.5 cm.) in thickness and admitting four fingers. The rim was attached to the left side of the uterus by a narrow pedicle in the manner of a circular flap hinged in the region of the left fornix. The pedicle was clamped and ligated and the cervical rim removed.

After delivery the mother and baby made satisfactory progress and were discharged on the tenth day of the puerperium. Six weeks after confinement the mother reported