Arch. Dis. Childh., 1966, **41**, 428.

Pneumonia due to Liquid Paraffin:

With Chemical Analysis

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The first description of oil aspiration pneumonia in man was by Laughlen in 1925. He described 4 cases diagnosed at necropsy: 3 of the patients were infants and 1 was an adult. In 2 cases the administration of liquid paraffin by mouth was incriminated and in the other 2 oily nasal drops had been used. Pinkerton (1927) described 6 cases diagnosed at necropsy, 5 were infants and 1 was a 6-year-old boy. Of these, 5 had suffered from chronic ill-health; a history of mineral oil ingestion was obtained in 3 cases. Ikeda (1935) reported 7 cases collected from a series of 101 consecutive necropsies on children, and gave a lucid account of the pathological changes. In at least 2 liquid paraffin was thought to be the causative agent. Brimblecombe, Crome, and Tizard (1951) described a case of liquid paraffin pneumonia in a boy of 8½ months, undiagnosed until necropsy. Bishop (1940) collected and reviewed 136, and Kaplan (1941) found references to 411 reported cases. More recently the American published reports were reviewed by Buechner and Strug (1956) and by Steinberg and Finby (1956). The majority of cases have not been diagnosed until necropsy.

There are a few references to cases diagnosed in life, but most of them were adults with pulmonary oil granulomas. Thus Wagner, Adler, and Fuller (1955) presented 5 cases of liquid paraffin granulomas in adults, and Siddons (1958) reported 3 cases of oil granuloma initially diagnosed as carcinoma of the bronchus; in one of Siddon's cases it was established that liquid paraffin had been ingested. Cotton and Lloyd (1960) described another adult case, in which liquid paraffin pneumonia and nocardial infection complicated a long-standing case of achalasia of the cardia.

In the majority of the recorded cases the diagnosis was made on purely histological grounds, and few authors have undertaken chemical extraction or attempted to identify the causative oil.

In the 40 years since Laughlen's original report many further cases have occurred, and despite warnings of the dangers of administering oily nasal drops and oral liquid paraffin to debilitated patients, especially infants, they continue to be seen. This paper records a case of liquid paraffin pneumonia in an infant with congenital abnormalities, and outlines a method of extraction and chemical identification that provides conclusive evidence of the nature of the oil.

Received January 3, 1966.

Case Report

The patient, a girl, was the first child of young parents. Her birth weight was 8 lb. 7 oz. (3,826 g.). The pregnancy and labour were uneventful. On examination soon after birth she was found to have oesophageal atresia, with an oesophago-tracheal fistula, and anal atresia. A thoracotomy was performed 24 hours after birth (Mr. A. R. Makey); the atretic part of the oesophagus was removed and continuity established. Apart from a slight chest infection post-operative recovery was satisfactory and the baby started to gain weight slowly. However, 3 weeks after the operation the thoracotomy wound became infected and had to be resutured. On the next day the baby collapsed and became grey after feeding through a tube. There were signs of respiratory embarrassment and a radiograph of the chest showed increased shadowing at the right apex. A radiograph of the chest a fortnight later showed that the lung fields had virtually cleared. Although the child recovered from this acute episode she had continual trouble with feeding, bottle-feeding never being successful, and until she died at 9 months she repeatedly coughed up considerable amounts of mucus, mainly after meals.

Soon after the oesophageal repair it was noticed that urine was passed only when suprapubic pressure was applied, and urinary infection was found. Investigations revealed marked bilateral hydronephrosis and dilated ureters. A right-sided Y-V ureteroplasty was performed at 3 months in an attempt to relieve the hydronephrosis. The urinary infection persisted, despite treatment with antibiotics in rotation.

From birth the baby had been intermittently constipated and frequent rectal wash-outs were necessary. Liquid paraffin was given by mouth from the age of 3

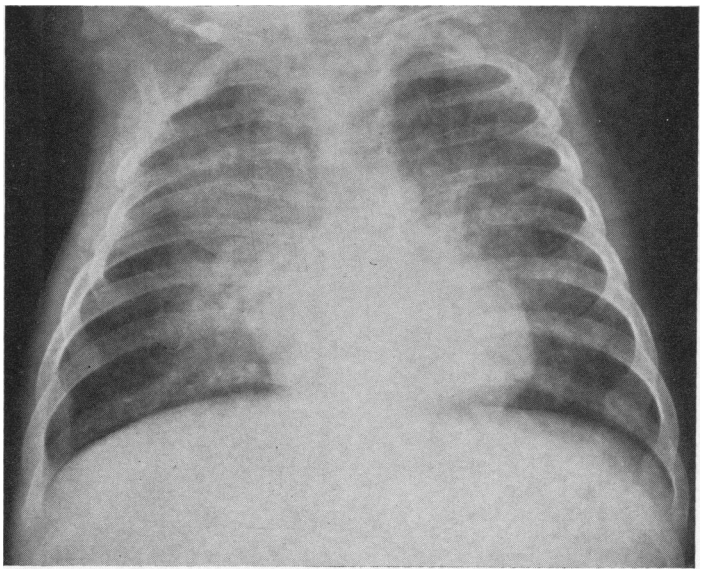

FIG. 1.—*Radiograph of chest one month before death.*

months, and this treatment was continued until death, with two breaks, of one week and three weeks, respectively. The dose varied from 8 ml. up to 45 ml. a day with an average of 25 ml. a day. Almost a month after the administration of liquid paraffin began the patient again became pyrexial with coughing and intermittent vomiting. From this time onwards her condition gradually deteriorated, with persistent urinary infection, an episode of acute gastro-enteritis at 5 months, and persistent chest infection. In the last month of her life she had intermittent pyrexia (up to 104° F. (40° C.)), and radiographs of the chest showed the picture of an aspiration pneumonia (Fig. 1). She died at the age of 9 months in severe respiratory embarrassment.

Necropsy. This revealed a well-nourished female infant (weight 7,224 g.). The larynx was normal. There was a small pouch (0·5 × 0·4 × 0·4 cm.) on the posterior aspect of the trachea 4·5 cm. below the vocal cords, which was thought to be the remains of the oesophago-tracheal fistula. The mucosa of the trachea and main bronchi was congested, and there was mucopus in the bronchial tree. Widespread grey-pink consolidation was present throughout the lungs, with a curious lobulated appearance. There was acute fibrino-purulent pleurisy, mainly on the right side, with fibrous adhesions at the bases. A purulent pleural effusion (40 ml.) was present on each side.

The right kidney was normal in size (4·5 × 2·5 × 1·5 cm.) but the left was small (3·5 × 2·5 × 1·5 cm.). The capsules stripped easily and the surface of the kidneys was smooth. Both kidneys were pale and there was blurring of the cortico-medullary demarcation. The cortex of the left kidney was thin (0·1 cm.); that of the right kidney was normal (0·3 cm.). The pelves and ureters were dilated. The wall of the bladder was thickened, but the bladder neck and both ureteric orifices were patent and the urethra was normal. The uterus and vagina were divided into two by a mid-line septum. The septate vagina and the rectum joined in a common recto-vaginal canal and external orifice. There was no separate anus.

Histological study. Paraffin sections of the lungs were stained with Mayer's haemalum and eosin-Y, van Gieson's stain, Weigert-French elastic stain, Foot's reticulin stain, periodic acid-Schiff, and Ziehl-Neelsen stain. Frozen sections of the lungs were stained with Sudan IV and Sudan black, Nile blue sulphate, and osmic acid. Frozen sections of kidney, liver, and adrenal were also stained with Sudan IV and Sudan black.

Lungs. Microscopical examination of the lungs revealed a diffuse interstitial pneumonia, with large numbers of oil-filled macrophages both in the interstitial tissue and lying free in the alveoli and bronchioles (Fig. 2). Many alveoli were almost filled with such cells (Fig. 3). In some macrophages the cytoplasm contained two or three small droplets of oil, while in others it was almost filled by a single large droplet. Multinucleated oil-containing macrophages were abundant. In some areas there was a serous exudate into alveoli. Much of the interstitial tissue was greatly thickened by an accumulation of histiocytes, lymphocytes, and plasma cells; scanty neutrophils were also present. This cellular reaction varied in intensity in different parts of the lungs, and was most marked in areas where there were large numbers of the oil-filled macrophages and serous exudate in the alveoli and bronchioles. The free oil droplets were stained pale orange-pink by Sudan IV; in

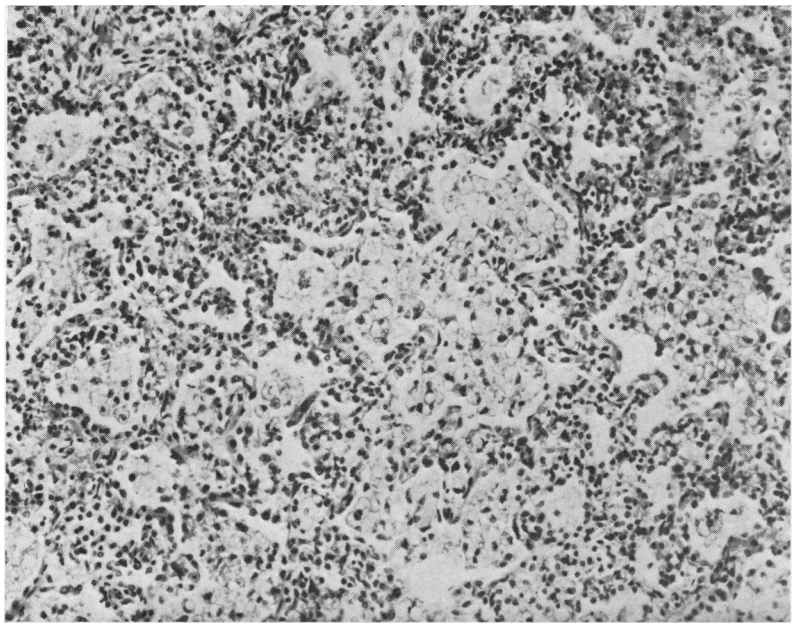

FIG. 2.—*Photomicrograph showing diffuse interstitial pneumonia with oil-laden macrophages in alveoli and interstitial tissue. (H. and E. × 100.)*

contrast, the droplets in the macrophages ranged from pale pink to colourless. No staining reaction was obtained with any of the other fat stains used. There was a slight increase in the number of reticulin fibres in the alveolar walls, but there was no increase in the amount of collagen or elastic tissue.

No oil droplets were seen in frozen sections of liver, kidney, or adrenal.

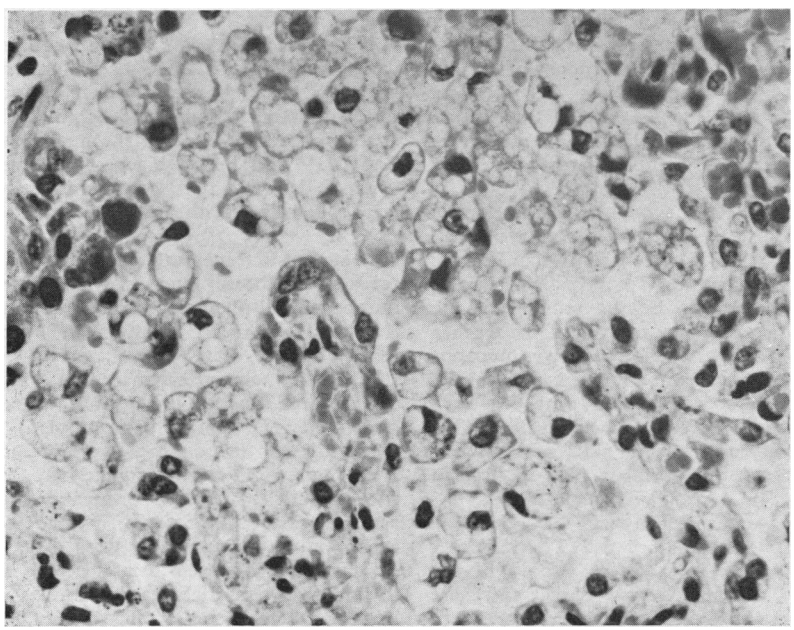

FIG. 3.—*High-power photomicrograph showing oil droplets in macrophages, and lying free within alveoli. (H. and E. × 336.)*

TABLE

Results of Chemical Extraction

	Lung from this Case	Control Lung	Cholesterol Stearate	Olive Oil	Liquid Paraffin B.P.
Weight of tissue	11·2	11·5	—	—	—
Weight of crude extract	1·009 (9·1%)	0·011 (0·098%)	—	—	—
Weight of material taken for saponification	1·009	0·011	0·213	0·290	0·879
Weight after purification in alumina column	0·979	0·004	0·032	0·002	0·895*
Weight after saponification and second purification	0·884	0·004	0·002	0·002	0·833
Weight after treatment with acid and third purification	0·775	—	—	—	0·567
Percentage yield of material taken for saponification	77	—	—	—	65

* High due to incomplete removal of petroleum ether. All weights in grams.

Chemical examination. Pieces of lung weighing altogether about 11 g. were homogenized with a small quantity of isotonic saline in an M.S.E. micro-emulsifier. The homogenates were shaken with 100 ml. petroleum ether and the mixture was filtered through 'celite' on a Büchner funnel to remove solid material and to break emulsions. The residue was washed well with petroleum ether which was then added to the first filtrate. The petroleum ether was separated from the aqueous layer, dried over anhydrous sodium sulphate, and evaporated to dryness ('first residue'). After weighing, the first residue was dissolved in 15 ml. petroleum ether and subjected to column chromatography using 6 g. alumina prepared with petroleum ether in a 1 cm. diameter tube. The flask was rinsed out twice with 5 ml. portions of petroleum ether which were also added to the column. Finally, the column was washed with 15 ml. fresh petroleum ether. The combined eluates (40 ml.) were evaporated to dryness in vacuum and the residue was weighed ('second residue'). The results are given in the Table.

Saponification. The second residue was dissolved in 8 ml. tetrahydro-furane. 2 ml. 2·5 N alcoholic KOH was added and the mixture was heated at 55° C. for 1 hour. A volume of 0·2 ml. distilled water was added and the mixture heated at 55° C. for a further 15 minutes. After cooling to room temperature the mixture was diluted with an equal volume of distilled water and extracted with 25 ml. petroleum ether. The petroleum ether extract was washed twice with 10 ml. distilled water, dried over sodium sulphate, and again subjected to chromatography as above. The residue obtained after removal of the solvent was weighed ('third residue').

Treatment with sulphuric acid. The third residue was transferred in ether to an 8 in. 'Pyrex' test-tube. 4 ml. concentrated sulphuric acid were added and the mixture was heated in a sand bath to 270° C. and kept at that temperature for 10 minutes. The tube was removed from the sand bath and allowed to cool to room temperature. The contents were black at this stage. Ice (about 10 g.) was added and when it had all melted the contents of the tube were transferred to a separating funnel and extracted with 25 ml. petroleum ether. This extract was washed with 10 ml. of 2N NaOH in distilled water, dried over sodium sulphate, and subjected to chromatography as described above. The residue obtained on removal of the petroleum ether from the eluate was weighed ('fourth residue').

Results and Discussion

The histological findings in the lungs were those of a lipid pneumonia and corresponded with those described by Ikeda (1937) as characteristic of oil-aspiration pneumonia. Ikeda mentioned the following oils and fats as possible agents in the production of such a pneumonia: cod liver oil, halibut liver oil, milk and cream, castor oil, iodized poppy seed oil, and liquid paraffin in its various forms. Of these he considered liquid paraffin and its various combinations, and cod liver oil, to be by far the most important.

In the case described in this paper there was a strong possibility that liquid paraffin was the aetiological agent concerned in view of the large doses (average 25 ml. daily) administered over a period of 6 months. The only other possible factor was milk fat, but on clinical grounds this seems unlikely as the pneumonic episode at the age of 3 weeks, which followed inhalation of milk, cleared rapidly, as was shown by radiological examination a fortnight later. Histological examination of lung sections showed the oil to be inert, for Sudan IV was the only fat-stain that it took up, and that rather poorly: this finding supported the view that the material was mineral oil. Another point in favour of its identification as a mineral oil was the persistent presence of large amounts of oil in the alveoli and interstitial tissue, either free in an emulsified state or in the macrophages, suggesting the inability of the body to metabolize it. It was thought that an attempt should be made to prove the assumption that the oil was liquid paraffin, particularly as this does not seem to have been done in previous cases. Brimblecombe *et al.* (1951) extracted 0·8 g. material from 7 g. lung, measured its specific gravity (0·85),

and showed that it did not react with a mixture of concentrated sulphuric acid and fuming nitric acid, but they did not carry out any more refined examination. It was possible to go further in the case described now and complete the identification of the oil.

In order to demonstrate conclusively that the material in the sections of the lungs was liquid paraffin, the oil was extracted, purified, and submitted to chemical and physical examination. Following homogenization of a representative piece of affected lung, 9% of its substance by weight could be extracted with petroleum ether, whereas pieces of normal lung yielded less than 0·1% of material extractable with petroleum ether. Of the material thus extracted from the specimen, 97% had the same chromotagraphic behaviour in alumina as liquid paraffin. The possibility of this material containing natural compounds such as cholesterol esters or neutral fats that might behave in the same way as mineral oil was eliminated by attempting to saponify it with alkali: the non-saponifiable fraction was again purified by chromatography. When cholesterol stearate and olive oil were taken through this procedure in parallel with the lung extract they proved to be completely removed; in contrast, Liquid Paraffin B.P. was completely recovered quantitatively. Finally, a sample of the lung extract and a sample of alkali-treated Liquid Paraffin B.P. were heated with concentrated sulphuric acid to 270° C. Both gave a good yield (77% and 65%, respectively; the difference in yield is within the limits of experimental error) of material with the same chromatographic properties as liquid paraffin. These final extracts had identical infrared absorption spectra (peaks at 2,925 cm.$^{-1}$, 2,860 cm.$^{-1}$, 1,460 cm.$^{-1}$, and 1,380 cm.$^{-1}$), (Fig. 4 and 5) and refractive index (lung extract = 1·4809, control liquid paraffin = 1·4816, at 17·50° C.; the difference, 0·0007, is negligible).

Thus the material extracted from the lung was shown to be liquid paraffin, and this is the first case in which this has been shown conclusively.

Ikeda divides lipid pneumonia into 'infantile' and 'adult' types; the infantile type, while occurring chiefly in infants, is not uncommon in debilitated older children and in elderly people. The aetiological agents are usually such oils as cod liver oil, milk, and liquid paraffin and its various combinations; the patient is either debilitated or in a mentally disturbed or comatose state in which artificial feeding is necessary, or suffers from some local condition such as cardiospasm, hiatus hernia, oesophageal obstruction, laryngeal paralysis, or tracheo-oesophageal fistula, which renders the swallowing mechanism defective, leading to spill-over into the trachea. In the case described in this paper, though the tracheo-oesophageal fistula was well repaired, the infant never swallowed well. It is thought that in these cases there is a defect in relaxation of the cardia resulting in a hold-up of food in the oesophagus. Clinically the condition is a slowly developing low-grade pneumonia with mild respiratory symptoms, which shows periodic exacer-

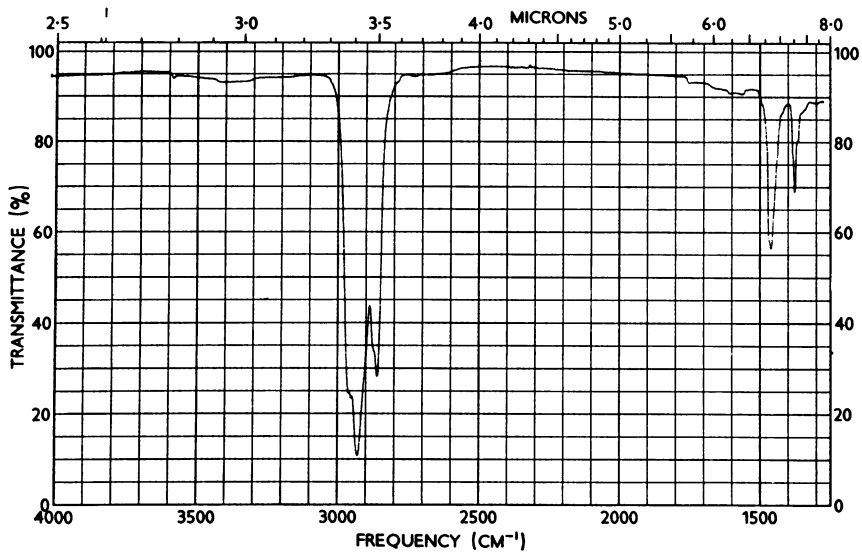

FIG. 4.—*Infrared spectrum of the lung extract from patient.*

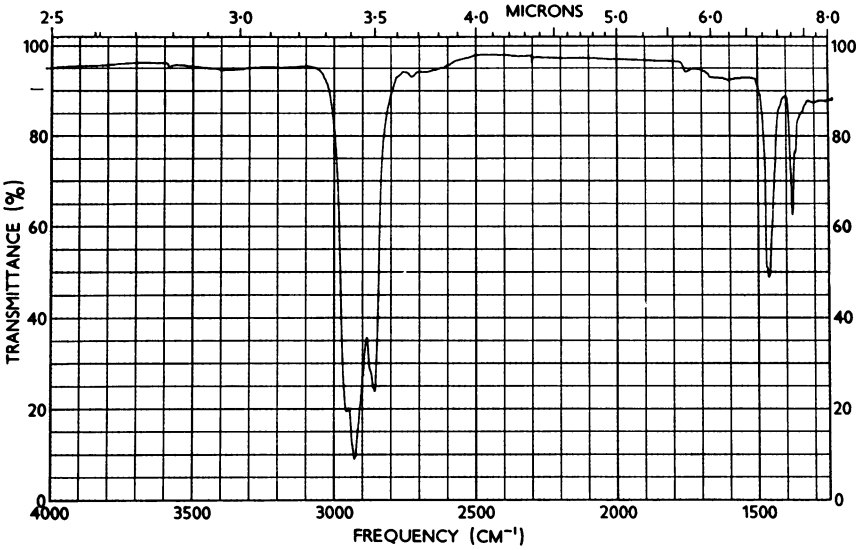

FIG. 5.—*Infrared spectrum of control sample of liquid paraffin.*

bation due to secondary infection or aspiration pneumonia.

Ikeda's adult type occurs usually among older otherwise fit persons, and often it is a result of long-continued self-administration of oil in large amounts, either by mouth or nasally. The typical lesion is the localized oil granuloma or paraffinoma, but there may be a more generalized granulomatous pneumonia. Although the basic cause is the same in the localized and generalized varieties, the physical condition of the patient plays a part in determining the degree of involvement of the lung. Thus, in debilitated patients there is a tendency for generalized lipid pneumonia to result, whereas a person in good general health is more likely to develop a localized granuloma.

A majority of cases of the infantile type are not diagnosed until necropsy, as in the case described.

Danger of fatal pneumonia from administration of liquid paraffin to infants. Although the case described here is an isolated example of lipid pneumonia proved to have been caused by the ingress of liquid paraffin into the air passages, it provides irrefutable proof that liquid paraffin can cause fatal lipid pneumonia. Clearly, liquid paraffin should not be administered to small infants, and perhaps even to older children, particularly if there is feeding difficulty.

Summary

A fatal case of lipid pneumonia is described, due to inhalation of liquid paraffin, in an infant who had had a congenital oesophageal atresia repaired. As the certain identification of this oil is not possible by histological or histochemical means, the material was extracted and purified, and its refractive index and infrared spectrum determined—these showed it to be liquid paraffin.

The published reports are reviewed briefly, and it is clear that the administration of liquid paraffin to infants, particularly those with feeding difficulty, is potentially dangerous.

I would like to thank Dr. Hugh Jolly and Mr. A. R. Makey for permission to publish this case history, Dr. Bernard Fox for his help and advice, Mr. J. Few for help with the chemical analysis, Dr. K. J. Packer of the University of East Anglia for carrying out the infrared spectroscopy, Mr. F. J. Humberstone and Mrs. H. Page for the histological preparations, and the staff of the Department of Medical Photography.

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Addendum

Since this paper was submitted for publication Johnston, Hock, and Buta (1965) have described a case of fatal ingestion of furniture polish, with characterization by gas chromatography and infrared spectroscopy. The technique used was similar to that described in this paper.

REFERENCE

Johnston, G. W., Hock, W. S., and Buta, W. C. (1965). Recovery of hydrocarbon from lung tissue in fatal ingestion of furniture polish. *Amer. J. clin. Path.*, **43**, 570.