methicillin or cloxacillin destroy these more rapidly than when cultured in broth. Sensitive strains cannot, of course, grow in high concentrations of these penicillins and therefore cannot be tested under comparable conditions. However, when such strains are pre-induced they too destroy methicillin and cloxacillin more rapidly than organisms cultured in broth. With all four strains of staphylococci used here, whatever method was used for inducing penicillinase, the rate of hydrolysis of methicillin and cloxacillin was a small fraction (1% or less) of the rate of hydrolysis of benzylpenicillin under comparable conditions. So far there is no evidence in these strains of a specific "methicillinase" or "cloxacillinase."

We are grateful to Dr. G. T. Stewart and Dr. K. R. Eriksen for sending their methicillin- and cloxacillin-resistant strains of *Staph. aureus*, to Beecham Research Laboratories for gifts

of methicillin and cloxacillin, and to Miss J. Ramsay for skilled technical assistance.

REFERENCES

- Ayliffe, G. A. J., Barber, M., and Waterworth, P. M. (1963). *Brit. med. J.*, **1**, 396.
 Bondi, A., De St. Phalle, M., Kornblum, J., and Moat, A. G. (1954). *Arch. Biochem.*, **53**, 348.
 Eriksen, K. R., and Erichsen, I. (1963). *Brit. med. J.*, **1**, 746.
 Heatley, N. G. (1944). *Biochem. J.*, **38**, 61.
 Jevons, M. P. (1961). *Brit. med. J.*, **1**, 124.
 Knox, R. (1960). *Ibid.*, **2**, 690.
 — (1961). *Ibid.*, **1**, 126.
 — and Smith, J. T. (1961). *Lancet*, **2**, 520.
 — (1962). *J. gen. Microbiol.*, **28**, 471.
 — (1963). *Brit. med. J.*, **1**, 396.
 Rolinson, G. N. (1961). *Ibid.*, **1**, 125.
 — (1963). *Ibid.*, **1**, 542.
 Steinman, H. G. (1961). *J. Bact.*, **81**, 895.
 Stewart, G. T., and Holt, R. J. (1963a). *Brit. med. J.*, **1**, 308.
 — (1963b). *Ibid.*, **1**, 465.
 — (1963c). *Ibid.*, **1**, 676.

MEDICINAL ARSENIC POISONING AND LUNG CANCER

BY

A. O. ROBSON,* M.B., M.R.C.P.

Resident Medical Officer, The Middlesex Hospital,
London

A. M. JELLIFFE, M.D., F.F.R., M.R.C.P., D.C.H.

Consultant Radiotherapist, The Middlesex Hospital, London;
and Mount Vernon Hospital, Northwood, Middlesex

For many centuries arsenic has been considered to be of medicinal, cosmetic, and forensic value. The first suggestion that the therapeutic administration of arsenic could lead to the development of cancer was made by Sir Jonathan Hutchinson in 1887, when he described five cases of skin cancer following the medicinal use of arsenic, and since then attempts have been made to relate cancer arising in other sites to the previous administration of arsenic. The causal relationship of arsenic to skin cancer is now well established, but the case for arsenic as a visceral carcinogen is unproved.

This report describes six previously unrecorded patients with arsenical skin changes following the therapeutic administration of arsenic, all of whom also developed lung cancers (Table I).

Case Reports

Case 1.—A woman aged 31 was admitted to hospital in September, 1956, with dyspnoea and productive cough for five months. Investigations showed an undifferentiated carcinoma of the left main bronchus, with metastases to the liver, axillary and supraclavicular lymph nodes, skull, pelvis, spine, and right femur. Skin nodules and jaundice appeared, and she died in six weeks. A post-mortem examination confirmed the clinical findings. As a girl in Dublin she was treated for many years with tonics for anaemia. In 1946 she noticed a "wart" below the left nipple. In 1952 "warts" developed on the hands, feet, and trunk. In May, 1956, an intra-epidermal carcinoma below the left nipple (Fig. 1) was subjected to biopsy and treated with a radiostrontium plaque. Typical arsenical keratoses of the hands, legs, and feet were also recorded. The arsenic content of hair was 3.5 p.p.m. (normal 0.3–0.7 p.p.m.). The patient had never smoked at any time.

Case 2.—A woman aged 45 was admitted to hospital in September, 1962, with pleurisy. Investigations showed an inoperable undifferentiated carcinoma of the right main bronchus. She had taken Fowler's solution for psoriasis intermittently over 15 years. At the time of admission arsenical keratoses of the palms and soles were present, and the arsenic content of the hair was 1.5 p.p.m. She had smoked 5 to 10 cigarettes daily for 20 years.

Case 3.—A man aged 54 had a pneumonectomy carried out elsewhere in 1955 for a poorly differentiated carcinoma of the left lung. In 1959 he died of heart failure. At post-mortem examination a localized poorly differentiated squamous-cell

carcinoma was found in the right lower lobe, possibly a new primary tumour. In 1920 he was treated for psoriasis for four years with Fowler's solution. In 1933 "warts" on the hands developed, and in 1944 an epithelioma of the left hand was excised. Over 11 years, six courses of superficial x rays and an excision were carried out for epitheliomas on the hands, fingers, and thigh. In 1955 three new lesions were excised—an epithelioma, an area of Bowen's disease, and an epithelioma with hypertrophy, pigmentation, and hyperkeratosis of the surrounding skin. Keratoses were present on the palms (Fig. 2) and soles, with pigmentation of the skin. The patient had been a "moderate" smoker for about 30 years.

Case 4.—A man aged 65, after dyspnoea for one month, was found to have a poorly differentiated carcinoma of the right

TABLE I.—Principal Features of New Cases Described

Case No.	Sex	Arsenic Administration	Skin Changes	Lung Cancer	Smoking Habits
1	F	Childhood, tonic for debility over many years	Age 21–31, multiple keratoses, intra-epidermal carcinoma	Age 31, undifferentiated carcinoma left main bronchus	Non-smoker
2	F	Age 28–43, Fowler's solution for psoriasis	Age 42–45, multiple keratoses	Age 45, undifferentiated carcinoma right main bronchus	5–10 cigarettes daily for 20 years
3	M	Age 15–19, Fowler's solution for psoriasis	Age 28–54, pigmentation, multiple keratoses, intra-epidermal and infiltrating epitheliomas	(1) Age 50, poorly differentiated carcinoma left main bronchus (2) Age 54, poorly differentiated carcinoma right lower lobe	"Moderate" cigarette smoker for 30 years
4	M	Age 38–41, Fowler's solution for psoriasis	Age 55–65, pigmentation, multiple keratoses, intra-epidermal epithelioma	Age 65, poorly differentiated squamous carcinoma right lung	1–2 pipes daily. No cigarettes
5	F	Age 10–13, tonic after rheumatic fever	Age 16, pigmentation. Age 39–47, multiple keratoses, and infiltrating intra-epidermal epitheliomas	Age 47, carcinoma right upper lobe	Non-smoker
6	F	Age 6–10, Fowler's solution for convulsions	Age 60, keratoses on palms and soles	Age 60, cerebral metastasis, poorly differentiated carcinoma right lung	Non-smoker

*Now at the Royal Victoria Infirmary, Newcastle upon Tyne.

main bronchus with enlarged supraclavicular lymph nodes. Improvement followed radiotherapy, but widespread metastases developed and he died three months after onset of illness. Twenty-seven years previously he was given Fowler's solution for three years for psoriasis. Ten years before admission warts were noticed on the palms of the hands. On admission there was a generalized pigmentation and hyperkeratosis, with well-marked keratoses on the palms and soles. An intradermal epithelioma was present on the neck (Fig. 3). He was not a

FIG. 1.—Case 1. Intra-epidermal epithelioma below nipple.

FIG. 2.—Case 3. Palms showing pigmentation, multiple keratoses, and superficial epitheliomas.

FIG. 3.—Case 4. Spotty pigmentation, keratoses, and intra-epidermal epithelioma on neck.

cigarette smoker, but he had smoked one or two pipes of tobacco daily for many years.

Case 5.—A woman aged 47 was admitted to hospital with right pleurisy. Investigations showed a large tumour mass in the right upper lobe, which could not be seen at bronchoscopy, but malignant cells were found in the sputum on each of several examinations. Radiotherapy was given. After an attack of rheumatic fever at the age of 10, she was given arsenic by mouth for three years. When 16 years old she developed pigmentation of the skin, and at the age of 39 hyperkeratoses began to appear. She had many intra-epidermal and invasive epitheliomas removed surgically during the five years before bronchial carcinoma was discovered. She had never smoked.

Case 6.—A woman aged 60. While being investigated for a brain tumour she was found to have a poorly differentiated carcinoma of the right lung. From the age of 6 to 10 she had received Fowler's solution for convulsions. Keratoses developed on the palms and soles; but they did not trouble her, and no attention was paid to them until she was found to have a lung cancer. The cerebral metastases responded rapidly to radiotherapy. She had never smoked.

Comment

The total amount of arsenic taken in each case is quite unknown. The period of administration varied considerably, ranging from 3 to 15 years, in most cases being given intermittently. It is obviously not possible to relate the age of onset of the lung cancer to the amount of arsenic ingested, but the three youngest patients certainly took arsenic for the longest overall period of time.

The latent period between starting to take arsenic and the clinical appearance of cancer of the lung varied between 17 and 54 years, with an average interval of 32 years (Table II).

TABLE II.—Duration of Arsenic Administration, Latent Interval Before Onset of Lung Cancer, and Age of Onset of Lung Cancer

Case No.	Duration of Arsenic Administration	Time from Starting Arsenic to Onset of Lung Cancer	Age at Onset of Lung Cancer
1	"Many years"	21 years	31 years
2	15 years	17 "	45 "
3	4 "	35 "	50 "
4	3 "	27 "	65 "
5	6 "	37 "	47 "
6	5 "	54 "	60 "

All the lung tumours—and there may have been seven primary growths among the six patients—were anaplastic in type, except for one (Case 5). Here it was not possible to obtain a biopsy, and the diagnosis was confirmed by the finding of malignant cells in the sputum.

Discussion

It is generally accepted that arsenic given by mouth can cause cancer of the skin. Of 137 cases collected in a review for the Medical Research Council (Neubauer, 1947), 88 patients received arsenic for skin diseases and 49 were treated with arsenic for varying conditions such as anaemia, epilepsy, asthma, and general ill-health. Sommers and McManus (1953) were able to collect a series of 26 cases of arsenical skin cancer, 8 of which had been reported by Franseen and Taylor (1934) and 20 of which followed medicinal arsenic.

The average age of onset of arsenical skin cancer is somewhat lower than that of non-arsenical skin cancer, which tends to be a disease of later life, occurring most commonly in the sixth and seventh decades. In Neubauer's (1947) series of arsenical skin cancer, 60% of the patients were under 50 years of age.

The true incidence of arsenical skin cancer cannot be estimated, but such cases are common. Arhelger and Kremen (1951) found 8 new cases among 110 patients with cutaneous malignancy over two years, and most dermatologists can recall seeing similar patients.

The role of arsenic as a visceral carcinogen has been under discussion for many years, and the subject is well reviewed by Buchanan (1962). The evidence is conflicting, but although arsenic cannot definitely be incriminated in this sinister role it would be wrong to dismiss such a possibility. The incidence of cancer following the administration of arsenic is quite unknown, and until reliable figures are available no valid conclusion can be drawn. It is difficult to relate the administration of arsenic to the later development of visceral cancer unless the well-recognized dermatological stigmata of arsenical poisoning are present or the arsenic content of the patient is known.

The association of carcinoma of the bronchus and arsenical dermatosis following the therapeutic administration of arsenic has previously been reported. Sommers and McManus (1953) refer to a patient with an inoperable bronchial carcinoma which developed 30 years after treatment with Fowler's solution for psoriasis. Three skin epitheliomas were also treated. Calnan (1954) reported the case of a man who developed arsenical keratoses, basal-cell carcinoma, and a bronchial carcinoma after the treatment of psoriasis with Fowler's solution, and in the subsequent discussion Forman (1954) recalled two lung cancers associated with basal-cell epitheliomata. Williamson (1960) recorded two bronchial carcinomas associated with arsenical skin cancer, but concluded that there was no evidence to show that the development of bronchial carcinoma was related to previous arsenic administration for psoriasis. The four patients referred to above who had a previous history of taking arsenic (Table III) were men, and no reference is made to their smoking habits.

TABLE III.—Principal Features of Previously Reported Cases

Authors	Sex	Arsenic Administration	Skin Changes	Lung Cancer	Smoking Habits
Sommers and McManus (1953)	M	Age 24, Fowler's solution for psoriasis. Duration not recorded	Age 54, three epitheliomas	Age 54, bronchial carcinoma, histology not recorded	Not recorded
Calnan (1954)	M	Age 24, Fowler's solution for psoriasis. Duration not recorded	Age ? keratoses, basal-cell carcinoma	Age 59, bronchial carcinoma, histology not recorded	"
Williamson, (1960)	M	Age 22-24, Fowler's solution for psoriasis	Age 29-50, pigmentation, keratoses	Age 50, anaplastic carcinoma	"
" "	M	Age 26-28, Fowler's solution for psoriasis	"Many years," keratoses, epithelioma	Age 58, squamous-cell carcinoma	"

While our cases do not prove a direct association between arsenic and visceral carcinomata, two particular features deserve further consideration. The smoking habits of this small group differ from the common pattern found in patients who develop carcinoma of the bronchus in this country. One patient smoked 5-10 cigarettes daily (Case 2), one was a light pipe smoker (Case 4), and three had never smoked (Cases 1, 5, and 6).

The sex incidence and age distribution of our group are also atypical. Four patients were women with undifferentiated carcinomas and three were under 50 years old. The unusual nature of this combination is indicated by

Kreyberg's (1962) unselected series of 600 cases of lung cancer, where there were eight women with undifferentiated carcinoma and none were under 50 years. One of our women was a light smoker (Case 2), and the fact that she developed a lung cancer after taking arsenic may be no more than an interesting coincidence, but in the case of the three non-smokers (Cases 1, 5, and 6) the coincidence becomes truly remarkable.

It is clear that the relationship between the therapeutic administration of arsenic and the later development of lung cancer is unproved, but it would seem reasonable to suggest that there was such an association in our patients. The existence of such a possibility is yet another reason to be added to those which are already generally accepted for abandoning the therapeutic use of this poison.

Summary

We believe that there may be a causal relationship between the therapeutic administration of inorganic arsenic and the later development of bronchial carcinoma.

Six previously unreported cases are described (four female and two male). Arsenic was prescribed for psoriasis, rheumatic fever, convulsions, or as a general tonic. The average latent period before the clinical onset of lung cancer was 32 years, and all the tumours were poorly differentiated carcinomas. All patients had skin manifestations of chronic ingestion of arsenic. Only two of them had ever smoked cigarettes.

A review of the recent English literature revealed four similar cases since 1953. It is generally accepted that arsenic administration may be followed by skin cancer. We suggest that a similar association with lung cancer may exist, but that it could be overlooked easily because of the long latent period.

We wish to thank Dr. F. H. Scadding, Dr. Neville Oswald, and Professor Sir Brian Windeyer for allowing us to include details of cases under their care. The department of medical illustration of the Middlesex Hospital provided the photographs.

REFERENCES

- Arhelger, S. W., and Kremen, A. J. (1951). *Surgery*, **30**, 977.
 Buchanan, W. D. (1962). *Toxicity of Arsenic Compounds*. Elsevier, Amsterdam.
 Calnan, C. D. (1954). *Proc. roy. Soc. Med.*, **47**, 405.
 Forman, L. (1954). In discussion with Calnan (1954).
 Franseen, C. C., and Taylor, G. W. (1934). *Amer. J. Cancer*, **22**, 287.
 Kreyberg, L. (1962). *Histological Lung Cancer Types*. Norwegian Univ. Press, Oslo.
 Neubauer, O. (1947). *Brit. J. Cancer*, **1**, 192.
 Sommers, S. C., and McManus, R. G. (1953). *Cancer (Philad.)*, **6**, 347.
 Williamson, A. W. R. (1960). *Guy's Hosp. Rep.*, **109**, 42.

After 44 years the Central Council for the Care of Cripples has officially changed its name to the Central Council for the Disabled. The council's offices remain at 34 Eccleston Square, London S.W.1. The council's administrator says: "Although in some ways we are sorry to make a break with our traditional name which has become well known to the public and the medical profession, it has become necessary to make the change. 'Cripple' no longer covers adequately the scope of our activities—'disabled' does. Our old name was out of touch with current thinking, since it underlined the more passive aspect of disability. To-day, thanks to advances in medicine and public opinion, the whole world is being opened to the disabled. Under our new name we will be pursuing new research and new ideas which promise to bring increased independence and greater chances of fulfilment to the lives of the physically handicapped."