Arsenic has been employed in the treatment of various diseases since the beginning of the Christian era, but its carcinogenic property was not suggested until 1820, when Paris wrote, "...it may, however, be of interest and useful to record an account of the pernicious influence of arsenical fumes upon organized human beings, as I have been enabled to ascertain in the copper-smelting works of Cornwall and Wales; this influence is very apparent in the condition both of the animals and vegetables in the vicinity; horses and cows commonly lose their hoofs, and the latter are often seen in the neighboring pastures crawling on their knees and not infrequently suffering from a cancerous affection in their rumps, whilst the milch cows, in addition to these miseries, are soon deprived of their milk. ... It deserves notice that the smelters are occasionally affected with a cancerous disease on the scrotum, similar to that which infests chimney-sweepers. ..." (30).

Keratoses were recognized as a consequence of the use of arsenic as early as 1868 by Erasmus Wilson. In describing the palmar and plantar surfaces of the hands and feet of his patient, he states, "... the cuticle is dry, harsh, and desquamating, and covered with hard, dry points, corresponding with the apertures of the sweat glands, which resemble minute corns" (42).

The etiological relationship between medicinal arsenic and carcinoma of the skin was first suggested in 1887 by Sir Jonathan Hutchinson when he reported several cases of carcinoma following the use of arsenic in the treatment of psoriasis (18). One of these cases had been reported by J. C. White of Boston two years earlier (40), but the important etiological rôle of arsenic had at that time been overlooked. Cases of carcinoma associated with psoriasis had been previously recorded by Pozzi in 1874 (31) and by Cartaz in 1877 (7), but the use of arsenic in these cases was not mentioned. It is more than likely, however, that these patients also received arsenic, since at that time it was a panacea for most skin diseases and was routinely used in the treatment of psoriasis. Even today, it is difficult to find a long-standing case of psoriasis that has not been treated with Fowler’s solution.

Geyer, in 1898 (13), made an exhaustive study of chronic arsenical affections among the inhabitants of Reichenstein, a small arsenic mining town in Prussia, where chronic arsenic poisoning obtained in numerous individuals through the use of drinking water contaminated by arsenic. An epidemic of arsenic poisoning from beer occurred in England in 1900, through arsenical contamination of the commercial...
sulphuric acid used in the manufacture of the invert sugar for brewing. This gave Brooke and Roberts an opportunity to record observations on a number of cases (5).

Since that time, several series of cases of arsenical keratoses and carcinomas have been collected from the literature. Dubreuilh, in 1910 (8), collected 19 cases of arsenical carcinoma with one of his own. The following year Nutt, Beattie, and Pye-Smith (26) collected 30 cases and added one of their own. Haagensen (14), in a review of the Memorial Hospital cases in New York in 1931, found 4 cases of carcinoma following the use of Fowler’s solution. McNeer (24) has recently reported 3 cases of carcinoma and one of keratoses from the same hospital. One of McNeer’s cases had previously been reported by Haagensen. Eller, in 1933 (10), stated that only 60 cases of carcinoma following arsenical keratoses had appeared in the literature, but he believed that there were many not reported.

Isolated cases of arsenical keratoses and carcinomas have appeared with considerable frequency in the literature. Though they are usually of medicinal origin, cases of occupational origin from fruit spraying, sheep dipping, taxidermy, etc., are occasionally reported.

The frequency with which we have encountered this condition among clinic patients has prompted us to review our cases of multiple keratoses and carcinomas of the skin in an attempt to ascertain how many could be attributed to the use of arsenic. As a result we have collected 14 cases in which the carcinomas of the skin appear to be of arsenical origin. One patient, with keratoses which were diagnosed as of arsenical origin, presented no lesions which had as yet progressed to carcinoma. Four additional selected cases of carcinoma are described as being possibly due to arsenic, and are illustrative of types sometimes classed in the literature as arsenical keratoses and carcinomas. Since we have taken the presence of hyperkeratoses of the palms and soles as our criterion of the culpability of arsenic, Cases 16 and 17, on this basis, represent carcinomas, and Cases 18 and 19 keratoses, with merely an incidental history of the administration of arsenic.

There is considerable discussion as to the classification of the latter groups of cases, i.e. as to whether they should be classified as being of arsenical origin, as being degenerating psoriasis with an incidental history of ingestion of arsenic, or in the group variously described by dermatologists as Bowen’s disease, extramammary Paget’s disease, or multiple superficial benign epitheliomata with an incidental arsenical history. There is occasional frank admission among dermatologists that the members of the latter group cannot be differentiated clinically; and an excellent brief has been held by Anderson for their absolute identity, clinically and microscopically, with arsenical keratoses and carcinomas. Indeed, one of Bowen’s original cases gave a history of the ingestion of arsenic (4).

It appears unnecessary to separate these lesions into groups other than basal-cell and squamous-cell carcinomas, and it is probably not justifiable to incriminate arsenic as the predisposing agent unless the
The patient has the characteristic arsenical hyperkeratoses of the palms and soles, or unless arsenic can be demonstrated microchemically in the lesions. The latter procedure has been successfully carried out by a few investigators (6, 27).

The part played by arsenic in the production of these malignant lesions has been disputed in some quarters on the ground that in many cases which have been called arsenical carcinoma there was a pre-existing chronic disorder and abnormality of the epithelium in which malignancy might arise, e.g. psoriasis, pemphigus, etc.; but the arsenical lesions have appeared after the ingestion of arsenic for such dissimilar affections as asthma, anemia, and epilepsy, in which the lesions could be in no way regarded as the consequence of the disease (16, 41).

That a metal may remain in the skin for an indefinite period of time is exemplified by the permanency of the cutaneous deposits of silver in argyria. Arsenic, however, unlike silver, acts as a cellular irritant to produce keratodermia, a necessary preliminary to epithelioma. The cellular irritation by arsenic predisposes to carcinoma in the keratoses it produces, since, as Schamberg has noted (33), other forms of keratoses such as clavi, histologically identical with arsenical keratoses and subject to similar chronic external irritation, never become malignant.

**Clinical Appearance of the Lesions**

The clinical appearance of the skin in chronic arsenical poisoning is quite characteristic. The palms of the hands and the soles of the feet are affected by a marked hyperkeratosis with clavus-like elevations, usually 2.0 to 5.0 mm. in diameter and of varying height. These often occur in the form of epidermal pegs which can be picked out of their keratotic beds. Superficial ulcers or fissures may occur where these horny lesions have been traumatized, and carcinomas may develop either in these ulcerated or fissured areas or in the hyperkeratotic areas themselves. Over the remainder of the body, flat, discrete, reddish, well delimited, scaling keratotic areas may occur, 0.5 to 10.0 cm. in diameter with raised pearly borders. These areas not infrequently heap up and undergo malignant changes. New lesions are not unlike heaped-up psoriatic patches and may, in fact, arise on their foundation.

These arsenical keratotic areas, in contradistinction to the common keratoses appearing in senility or in weather-beaten individuals, are not ordinarily restricted to the exposed parts of the body, i.e. face, ears, and dorsum of the hands, but, with the exception of the palms, characteristically appear on unexposed parts of the body. The skin of the upper half of the trunk is commonly affected, the lower half but rarely.

Varying degrees of pigmentation of the skin, usually of the "rain-drop" type, may accompany these arsenical lesions; but only one of our patients (Case No. 13) showed pigmentary changes in any noticeable degree.

It has been suggested that leukoplakia of the mouth may accompany arsenical lesions of the skin, but we have not observed this in any of our cases.
Pathology

Anderson (1) has already called attention to the fact that, although arsenical carcinomas are commonly thought to be only of the squamous type, the basal-cell type of carcinoma frequently appears. Milch (25) has again recently stated, however, that squamous-cell epithelioma with typical pearl formation has invariably been reported by observers of this condition.

Among 25 microscopic sections from primary carcinomas in this series available for examination, Dr. Shields Warren has classified 9 as basal-cell carcinoma; 9 as epidermoid carcinoma, grade I; 4 as epidermoid carcinoma, grade II; and one as a mixed basal and epidermoid carcinoma. These gradings were made on a three-group basis in the order of increasing degrees of malignancy (11). One specimen from the Massachusetts General Hospital was classified by Dr. T. B. Mallory as epidermoid carcinoma, grade II. It will be seen, therefore, that the more slowly growing types of carcinoma predominate.

Bland-Sutton (3) at one time stated that carcinoma of arsenical origin did not metastasize to the regional lymph nodes, but several cases have already been reported in refutation of this opinion. In our series, seven patients developed regional metastases from nine lesions. Of the primary lesions from which the metastases arose, six were graded I, epidermoid carcinoma, two were graded II, and one specimen examined elsewhere was an ungraded epidermoid carcinoma. Five of the metastatic lesions were confirmed by histological examination.

Differential Diagnosis

The presence of multiple horny keratoses on the palms of the hands and soles of the feet is usually recognized as being pathognomonic of chronic arsenical poisoning. In the presence of keratoses or epitheliomas on unexposed parts of the body, a history of medicinal ingestion of or occupational exposure to arsenic can often be elicited; but we are of the opinion that keratoses of the palms and soles are essential for an unequivocal diagnosis unless arsenic can be demonstrated microchemically in the lesions. Hyperkeratoses of the palms and soles are probably never seen in uncomplicated psoriasis. However, even in the absence of the characteristic palmar and plantar lesions, the microchemical method may still differentiate between degenerated psoriatic lesions on the trunk and lesions of arsenical origin.

Multiple keratoses or carcinomas are frequently seen on exposed surfaces alone, i.e. face, ears, and dorsum of the hands. These do not suggest an arsenical origin.

Both the organic and inorganic forms of arsenic may produce an acute dermatitis, but such lesions are distinct both in their appearance and in their acute or subacute course and never enter into a differential consideration with the lesions here described.
ARSENICAL KERATOSES AND CARCINOMAS

CHEMICAL PATHOLOGY

Osborne (27), extending the work of Brünnauer (6), used a modification of a method introduced by Justus in 1905 (19) to precipitate arsenic as arsenic trisulphide crystals in tissue sections prepared from arsenical keratoses. He found that the largest arsenic deposits were in the papillae of the corium and in the basal layers of the epidermis. The coil glands and ducts contained large quantities of arsenic; and considerable amounts were found in the hair follicles, including all the layers of the sheath and the hair itself. It had previously been shown that arsenical poisoning could be demonstrated, many years after the source had been removed, by chemical analysis of the hair or even the nails for arsenic, and especially the more slowly growing pubic hair (17).

Osborne suggested that the mechanism of the production of arsenical keratoses seemed to be the speeding up of the keratinization cycle by the deposit of an irritant in the form of arsenic in the upper corium, papillae, and epidermis, and that the stimulation of the basal layer in the same manner might well offer the explanation for the formation of carcinomas.

According to Solis-Cohen and Oithens (34), the combination of arsenic with the tissues is apparently effected by its substitution for phosphorus in the lecithin molecule. This breaks up slowly, and elimination may be a prolonged process.

All compounds of arsenic do not appear to be equally carcinogenic. Edmunds and Gunn offer a partial explanation for this in the following statement. "The action being due to the ion and not to the element, it necessarily follows that compounds from which the ion is not liberated do not induce the arsenic action, or do so only when they are changed to bodies which can dissociate the arsenious acid ion. Thus organic arsenic combinations in which the metallic atom is directly attached to carbon are only feebly poisonous, but in the course of time seem to be changed to arsenious acid in the tissues, and then cause typical poisoning (9)." Arsphenamine has been shown in rabbits to be rapidly eliminated, with no evidence of appreciable storage, when given in therapeutic doses (29). A combination of these factors probably accounts for the comparative rarity of chronic arsenical lesions after the administration of arsphenamine.

ASSOCIATED CARCINOMA OF THE INTERNAL ORGANS

In view of the carcinogenic effect of arsenic in the skin, it became interesting to note whether any of the patients with arsenical carcinoma subsequently developed primary carcinoma of any of the internal organs, especially at other sites of excretion or storage.

Excretion of arsenic is said to occur by all the usual channels; urine, feces, sweat, milk, and epithelium of the skin (35). Underhill found the human liver to have stored arsenic in the highest concentration
after chronic arsenic poisoning. The stomach wall, intestinal wall, and kidneys were next in order (38).

One of our patients (Case No. 4) died with a lesion which by x-ray examination suggested a carcinoma of the esophagus. There was a mass in the region of the thyroid gland, however, which may have been the primary source. A second patient (Case No. 9) with arsenical keratoses, but without carcinoma of the skin, was found by follow-up to have died with a carcinoma of the pancreas. This had been verified by operation alone. Neither of these two lesions occurred at sites of excretion and they give but meager evidence for the occurrence of carcinoma of the internal organs.

Haagensen (14) stated that no carcinoma of the internal organs had been found in persons with arsenical carcinoma of the skin and, in the absence of such findings, suggested that the controversy over the etiology of the Schneeberg miner’s lung carcinoma be settled in favor of its origin from the radio-active air of the mines rather than from the arsenic in the mine ore. However, one of Hutchinson’s original patients was subsequently reported by Nutt, Beattie and Pye-Smith to have died of carcinoma of the stomach (26). We have been unable to find any other series in which this question has been investigated.
ARSENICAL KERATOSES AND CARCINOMAS

ABSTRACTS OF CASES

A. Cases Certainly of Arsenical Origin

This group includes those of our cases in which a history of exposure to arsenic was obtained and in which the characteristic hyperkeratoses of the palms and soles were observed.

Case No. 1 (A. E., H. M. H. 28: 95) (Fig. 1): A fifty-nine-year-old fruit farmer was first seen in January 1928. For thirty or more years he had sprayed his fruit almost every day during the summer months, in early years with Paris green, later with lead arsenate liquid, and often stood in a cloud of arsenic spray during his work. At entry he had an ulcerated, carcinomatous growth on the ear and a second nodular, carcinomatous growth on the upper lip. There were numerous crusted and scaling lesions over the body varying from 1 to 3 cm. in diameter. The palms of the hands and the soles of the feet were covered with innumerable hyperkeratotic areas. The warty lesions on the hands had been present as long as the patient could remember, but the lesions on the body first appeared about nineteen years before entry. Excision of a basal-cell carcinoma of the ear was done in February 1928, and five applications of radium were made to areas on the body during the following nine months. The patient then failed to return until April 1931, at which time he showed a recurrence of the carcinoma of the ear and new carcinomatous areas of the left arm and right leg. These were all excised and all proved to be basal-cell lesions. During the past two years the patient has been kept under observation at intervals of about two months. At each visit all the areas suspected of undergoing malignant changes have been treated with radium. To date he has had about 80 applications of radium. With this procedure all the areas have been kept under control. Since his first visit to the clinic, the patient has carefully avoided all contact with arsenic sprays. He could not recall ever having taken any medicine that might have contained arsenic.

Case No. 2 (C. C., H. M. H. 18: 750) (Figs. 2 and 3): A fifty-five-year-old market worker was first seen in December 1918. He had been given a course of arsenic by mouth over three or four years for a dermatitis of the scalp. Keratotic lesions appeared on the
hands and feet shortly after the arsenic had been discontinued. About eighteen months before entry he had received several intravenous injections of "606," and a few months before entry he had been given some medicine for the keratoses which he thought contained arsenic. When he was first seen, both palms were covered with warty excrescences and degenerative crusting and scaling patches in various stages of development, some with only a moderate amount of thickening, others beginning to ulcerate. There were a few scattered lesions over the back, shoulders, and chest, somewhat larger than the keratotic spots on the hands and more scaling and crusting in character. At the base of the left thumb was an irregular, hard, reddish, granular, slightly furrowed ulcer, $5 \times 5.5$ cm., with everted, roll-like borders and an indurated base covered by a milky discharge. There was a similar lesion on the second finger at the proximal interphalangeal joint, measuring 4 cm. in diameter, and another lying just below the internal malleolus of the right foot, 5 cm. in diameter. The latter was somewhat papillomatous in character. There was another area on the left foot between the toes, and a crusting patch on either side of the

![Fig. 3. Case No. 2: Multiple Arsenical Keratoses and a Carcinoma of the Right Foot](image-url)

serotum. The index finger of the left hand was amputated, and excisions were made of the lesions at the base of the thumb and on the heel. All showed epidermoid carcinoma, grade I, histologically. Radium treatment of the excised areas on the heel and at the base of the thumb followed, but recurrence occurred in spite of this. Node enlargements appeared in both groins and also in the axillae and neck. The patient died at home in January 1920.

**Case No. 3 (F. C., H. M. H. 26: 179):** A fifty-one-year-old janitor was first seen in the clinic in February 1926. The only exposure to arsenic that the patient could recall was during fruit spraying twenty-seven years previously. At entry he had a warty, irregular, ulcerated carcinoma on the left side of the neck, which had been present for more than a year. There was a similar growth on the anterior surface of the right shoulder. Several other keratotic areas were present on the trunk, and the palms and soles presented the warty keratoses characteristic of chronic arsenical poisoning. The lesions on the neck and shoulder were destroyed with radium. Subsequently multiple new areas appeared over the trunk, and more than thirty applications of radium were made to as many areas. Among these new areas were two which were diagnosed clini-
cally as having become carcinomatous. Unfortunately, no pathological reports are re-
corded on this patient. He is still under observation and free from carcinoma.

Case No. 4 (I. D., H. M. H. 23: 144): A sixty-seven-year-old housewife was first
seen in February 1923. She had taken Fowler's solution forty years previously, for "a
considerable time." Following this, calluses appeared on the hands; later, rough spots
appeared on the body. Seven years ago a small red spot developed over the crest of the
right ilium and gradually increased in size until at admission there was an irregular,
raised, ulcerated growth 3 × 5 cm. at the site. There were many keratotic areas on the
palms and a keratotic area on the left upper arm. Radium was applied to the keratotic
area on the arm and the lesion over the ilium was excised. The latter proved to be epider-
moid carcinoma, grade I, histologically. In September 1933, a new papillary lesion on
the neck was destroyed with radium. During the succeeding four and a half years,
seven additional heaped-up keratotic areas appeared on the body and were treated with
radium. In April 1928, a lesion diagnosed clinically as epidermoid carcinoma appeared
on the left thigh and was destroyed with radium. Five additional keratotic areas were
treated during the following eighteen months. In February 1931, the patient returned to
the clinic with marked anemia, malnutrition, and difficulty in swallowing foods. A mass
4 × 2 cm. was palpable under the lower end of the right sternocleidomastoid muscle; it
was thought to arise in the thyroid gland. An x-ray report at this time stated: "There
is a ragged filling defect in the esophagus just beneath the clavicle. This has the ap-
pearance of carcinoma. There is apparently a diverticulum about three inches lower in
the esophagus." The patient died suddenly at home in June 1931, and an autopsy was
not done.

Case No. 5 (P. McD., H. M. H. 25: 349): A sixty-three-year-old telephone lineman
was first seen in March 1925. Ten or fifteen years before entry the patient had been
given Fowler's solution in doses of 5 min. t. i. d. by a dermatologist for "large, scaly, red
spots" on the body. He had had the prescription refilled by his druggist, and continued
taking the solution for about two years. At the time of admission, there were multiple
keratotic areas over the palms of the hands. No description of the soles of the feet was
recorded. Over the left scapula was a lesion 7 cm. in diameter, with an indurated base
and raised edges. It had been ulcerated for four months. Over both body and extre-
meties were multiple red, slightly raised areas varying in size from 1 to 8 cm. in
diameter, some covered by dry thin scales, and some by thin crusts. The ulcerated lesion
on the back was excised and by microscopic examination was shown to be an epidermoid
carcinoma, grade I. Twenty-seven other areas on the back, thigh, and shoulders were
treated with radium during the following seven months. In January 1926, a recurrence
of the carcinoma of the back was excised, and in the following month metastases in the
left axilla were discovered and treated with x-rays. In April 1926, a recurrent carcinoma
in the skin between the axilla and the original lesion was treated with low-voltage x-rays.
In December 1926, additional recurrent areas of carcinoma of the back were excised and a
dissection of the lymph nodes of the left axilla was done. The lymph nodes showed the
presence of epidermoid carcinoma, grade I, histologically. Ten additional areas on the
body were treated with radium. The patient died at home in March 1928, after recurrent
carcinoma had appeared in the back, and metastases in the supraclavicular nodes.

Case No. 6 (L. W., H. M. H. 23: 691): A fifty-year-old housewife was first seen in
June 1923. About twenty-nine years previously she had taken, among many other medi-
cines, about a quart of "Dr. Greene's Nervine," which contained arsenic. At first it
had been taken for nervousness, later for epilepsy. Two fingers of the left hand had
been amputated, and an axillary dissection done six years previously at another hospital.
The microscopic report was epidermoid carcinoma with axillary metastasis. At entry,
there were innumerable keratoses on the body, hands, and feet. A papillary carcinoma
involved the middle and distal phalanges of the index finger of the left hand. There was
a carcinoma on the right side of the neck which had arisen in a keratosis and there was an
area suspicious of carcinoma on the sole of the left foot. A large keratotic area about
8 cm. in diameter was present on the mons pubis. Amputation of the left index finger
was done and epidermoid carcinoma, grade I, found. During the succeeding two years
over one hundred applications of radium were made to as many areas. In January 1925,
the nodes in the left axilla were found to be enlarged to the size of a fist. All new areas were kept under control by means of treatment with radium and low-voltage x-radiation, but the mass in the axilla continued to grow in spite of high-voltage x-ray treatment, and the patient died at home in November 1925.

Case No. 7 (A. G., P. H. 4326): A fifty-one-year-old jewelry worker, who handled gold plate and soldering fluids, was first seen in March 1932. He gave an indefinite history of having taken arsenic for two months at one time. At entry, he had numerous keratotic areas over the body, hands, and feet. Some were ulcerating and crustng. The patient stated that he had had a rough skin rash for more than twenty years. Twenty months before admission he had noticed a lump in the left groin, and after a year's observation by his physician, the lump was removed. The pathological report was epidermoid carcinoma, grade II. At entry, the entire left leg was markedly edematous. There was an old healed scar in the groin, and by rectal examination a hard, fixed, irregular mass was found bulging from the left side of pelvis. In spite of x-ray treatments, the patient steadily failed and died at home in June 1932.

![Figure 4. Case 10: Arsenical Keratoses on Hands](image)

Case No. 8 (R. A., H. M. H. 25: 27): A fifty-three-year-old storekeeper, previously a telegraph operator, was first seen in January 1925. Fifteen years before entry he had been given Fowler's solution by his local physician in doses of six drops three times a day for an eruption on the body. On repeated prescriptions from his physician, the patient continued to take the arsenic, off and on, until his first visit to the clinic. Eight months before entry numerous wart-like areas had appeared on the hands, and the palms and soles were now covered with numerous hyperkeratotic areas. One of the hyperkeratoses at the base of the left thumb had become ulcerated and at entry was about one cm. in diameter. A few keratoses were present on the face. The lesion at the base of the thumb was excised by the patient's local physician and was found not to be malignant. Thirteen applications of radium were made during the following three years and all the keratotic areas threatening malignant changes were destroyed. The patient then failed to return for three years, and at his next visit, in April 1933, a carcinoma had developed on the ring finger of the left hand about one cm. in diameter. Several large, thickened keratotic areas were found scattered over the back. Excision of the lesion on the finger showed it to be a mixed basal and epidermoid carcinoma. During the past year the patient has been made to recognize the importance of frequent observations and prophylactic radiation, and thirty-four radium applications have been made to suspicious areas.
No new carcinomas have developed. Several fissured keratoses over the joints of the fingers have been destroyed with radium to the increased comfort of the patient.

**Case No. 9** (F. L., H. M. H. 21: 284): A forty-seven-year-old machinist was first seen in March 1921 with multiple keratoses and warty growths on the palms of both hands. A similar but less marked condition was present on the soles of both feet. During his youth, the patient had been given arsenic "over quite a period of time" for epileptic fits, but had taken none for the past twenty years. The keratoses had appeared on the hands and feet shortly after he had stopped taking arsenic. Fourteen applications of radium were made to the keratotic lesions here, and several lesions were fulgurated elsewhere. Two months later the patient wrote that the lesions had all stopped growing and had dried up. He was not seen here again, but a recent letter from his local physician states that a carcinoma of the body of the pancreas was found at operation in May 1930, and that death occurred in August 1930 after a long period of obstructive jaundice.

**Case No. 10** (C. D., Tumor Clinic, Massachusetts General Hospital E. S. 296183.) (Fig. 4): A thirty-seven-year-old plumber was first seen in January 1929. He had had psoriasis for many years, for which he had taken Fowler's solution, up to 15 minims, three times a day beginning in 1915 and continuing until 1925, with brief omissions about twice a year. Lesions of the palms and soles began to appear in 1923, and ulceration began in some of these about six months before admission. At admission the patient had marked hyperkeratoses of the palms and soles and also of the dorsum of the hands. There was an ulcerated carcinoma the size of a bean on the dorsum of the middle metacarpophalangeal joint. The keratoses of the hand terminated at about the cuff line, but there were scattered lesions over the trunk described as psoriatic. The carcinoma of the hand was excised at admission and found microscopically to be an epidermoid carcinoma, grade II. The patient has since been followed at the Tumor Clinic at the Massachusetts General Hospital and, by treatment with X-ray and radium to several areas, has been kept free of further malignant disease. Of incidental interest is the fact that all his siblings had psoriasis also.

**B. Cases Probably of Arsenical Origin**

This group includes those of our cases in which keratoses of the palms and soles with the characteristic features of those produced by arsenic ingestion were observed, but in which a definite history of exposure to arsenic was not obtained.

**Case No. 11** (L. E., H. M. H. 25: 1125; P. H. 2556): A sixty-five-year-old housewife was first seen in September 1925, with a basal-cell carcinoma overlying the right scapula, 4 cm. in diameter, and raised about 1 cm. from the skin surface. There was a flat keratotic lesion about 3 cm. in diameter on the left shoulder, and a second flat, red, keratotic area on the back, measuring 5 by 3 cm. There were hyperkeratoses of the soles of the feet and the palms of the hands, with many small keratotic lesions scattered over the body. These lesions had been present for nearly thirty years. Several applications of radium were made to the lesions on the body, followed by low-voltage X-ray treatments until June 1927. In September 1930, the patient was operated upon for an epidermoid carcinoma of the vulva, grade II, metastatic to the groin, but died ten days later. An autopsy was performed. In spite of the fact that in the history no mention was made of exposure to arsenic, the diagnosis of arsenical keratoses with malignant degeneration was concurred in by a dermatological consultant.

**Case No. 12** (A. K., H. M. H. 19: 195): A forty-five-year-old baker, formerly a knife-grinder, was first seen in March 1919, with both palms and soles covered with innumerable keratoses, varying in diameter from 2 mm. to 1 cm. These had been present in some degree for about twenty years. There were no keratoses on the face or neck, but several on the trunk, arms, and legs. A postoperative defect was present on the sole of the left foot at the site of a recent excision of a lesion reported pathologically as being epidermoid carcinoma. An area of characteristic carcinomatous degeneration was present at the base of the right thumb, and the lymph nodes of the right axilla were questionably
involved in the disease. Biopsy of the lesion on the thumb showed it to be an epidermoid carcinoma, grade I. There were two heaped-up keratotic areas with central craters on the sole of the left foot. Several radium treatments were given, with some benefit. Later, an enlarged lymph node appeared in the left groin, and an excision of the ulcerated area on the left foot together with a dissection of the lymph nodes of the groin was made. The pathological report on both the lesion on the foot and the nodes of the groin was epidermoid carcinoma, grade I. By February 1920, the lymph nodes of the right axilla had become demonstrably enlarged, and an additional carcinomatous area had appeared on the right foot. Three additional radium treatments failed to check the progress of the disease, and the patient died at home in June 1920, with multiple metastases. No history of medicinal or occupational exposure to arsenic could be elicited.

FIG. 5. CASE NO. 13: ARSENICAL KERATOSSES AND SPONTANEOUS AMPUTATION OF RIGHT INDEX FINGER FROM CARCINOMA

CASE No. 13 (A. L., P. H. 6803) (Fig. 5): A fifty-six-year-old millworker, who had previously been a weaver for thirty years, was first seen in September 1933. Thirteen years previously he had received twenty intravenous injections and two intramuscular injections for "weakness." He denied venereal infection by name and symptom, and stated that an examination of his blood just prior to the injections was "negative." Following the injections he was given a medicine in drops by mouth for a year and a half. Examination showed many small pigmented areas of the "raindrop type" over the entire body; and there was marked hyperkeratotic thickening of the palms of both hands and the soles of the feet, which the patient stated had been present for about ten years. A few scattered keratotic areas up to 3 cm. in diameter were present on the trunk and arms. A hard sore appeared on the right index finger seven years before entry, and the finger had slowly undergone spontaneous amputation. The index finger was reamputated.
surgically and a dissection of the axilla made. The pathological report was epidermoid carcinoma, grade I, of the finger, but there was neither gross nor microscopic evidence of carcinoma in the axillary lymph nodes. The patient has now several new keratotic areas on the body which are being carefully observed.

**Case No. 14 (W. S., H. M. H. 18: 420):** A forty-six-year-old farmer was first seen in June 1918. He gave a history of having taken many medicines over a fifteen-year period, but did not know specifically whether any of them had contained arsenic. At entry he presented unhealed amputation stumps of the right ring and little fingers, which had been removed for carcinoma, the right finger eight weeks previously and the little finger seven months previously. There had been a recurrence of the disease in the stumps and at the base of the middle finger. The palms of the hands were “literally gloved in keratotic lesions,” a few of which were slightly ulcerated. Numerous keratoses were present on the soles of the feet, and a few were scattered over the body. A dermatological consultant reported after examination that the lesions “would suggest arsenical keratoses and, in fact, nothing else.” Two radium treatments were given to keratoses, and partial amputation of the hand was advised. The latter was done by the patient’s family physician three months later, and the pathological report was returned as carcinoma. Ten months after this a mass of carcinomatous lymph nodes was removed from the right axilla by the same physician. There was recurrence of the carcinoma in both stump and axilla, cervical metastases appeared, and the patient died at home in May 1920.

**Case No. 15 (S. L., P. H. 3810):** An eighty-year-old retired meat dealer was first seen in October 1931 with lesions all over the body, varying from small keratoses to large epidermoid carcinomas 6 cm. in diameter, with ulcerated centers. There was one such large carcinoma on the scalp and two on the back. There was bilateral enlargement of the lymph nodes both of the groins and axillae. The tonsils were so large that they almost closed the pharynx. The spleen was not palpable. The palms and soles showed the warty keratinization characteristic of arsenical lesions. The white blood cell count was 107,400, with 94 per cent lymphocytes. A diagnosis of carcinoma arising in arsenical keratoses was made, together with a diagnosis of an atypical lymphatic leukemia. Biopsy of the scalp and neck lesions showed both to be epidermoid carcinoma, grade II. X-ray treatments were given to the groins and axillae. The carcinomatous lesions were treated with x-rays primarily, and secondarily with radium. Following a temporary improvement, the patient grew worse and died at home in June 1932. The patient was unable to give a history, but it seemed likely that he had received arsenic therapeutically in connection with his leukemia.

**C. Cases Possibly of Arsenical Origin**

This group includes those of our cases in which there was a history of exposure to arsenic, but in which examination showed only keratoses of the body, without plantar or palmar keratoses.

**Case No. 16 (W. C., H. M. H. 27: 649):** A sixty-three-year-old shoemaker was first seen in May 1927. He “had been in the habit of taking Fowler’s solution for asthma.” Overlying the first thoracic vertebra was an indurated lesion 3 cm. in diameter, infiltrating quite deeply, slightly ulcerated, and of fourteen months’ duration. The lesion was excised and found on microscopic examination to be a basal-cell carcinoma of low malignancy. A suspected recurrence was excised seventeen months later and diagnosed microscopically as verruca. Two keratoses in the temporal region and one over the scar of the previous excisions were treated with radium between 1929 and 1931 in six applications. The lesions were well healed except for slight scaling when last seen in April 1932. The patient has since failed to return or to answer follow-up letters.

**Case No. 17 (A. C., H. M. H. 21: 1314, P. H. 428):** A fifty-three-year-old housewife was first seen in November 1921. Beginning at the age of twenty-one, she had taken “arsenic” off and on for three years, in the treatment of psoriasis. At the age of forty-three she had taken it irregularly for two or three months. At entry, an indurated new growth, about 3 cm. in diameter, was present on the forehead, a similar growth on the
left side of the tip of the nose, and a third in the left temporal region. On the lateral surface of the right upper arm was a fungating new growth 10 cm. in diameter, centrally ulcerated, but not very adherent to the deeper structures. There was a large warty lesion about 5 cm. in diameter on the right arm, surrounded by an eczematous area. Several keratotic areas were found on the chest, back, and abdomen, and several lesions which were definitely those of psoriasis. The lesions on the left upper arm and nose had appeared about two years before the patient was seen in the clinic; the remainder, except for the chronic psoriatic patches, had appeared in the interim. The lesion on the left upper arm, a basal-cell carcinoma, was treated by excision, and the lesions on the forehead, nose, temple, and left neck by radium application. The operative wound on the left arm healed well and the patient did not reappear for eight months. The lesion on the right upper arm had then become frankly carcinomatous and was excised and later grafted with skin. The pathological report was epithelioma adenoides cysticum. The area on the nose was given an additional radium treatment, and two areas on the left hand and left cheek were also treated. In March 1928 the patient was seen at Pondville Hospital with two large new lesions on the hip. Both were excised, and the pathological report on both was given as rapidly growing basal-cell carcinoma. Additional radiation was given to the nose, forehead, ear, and neck until September 1931. Subsequently treatment was with x-rays by a local physician. The Town Clerk reports that the patient died at home in January 1934, of "metastatic carcinoma from the nose." No description was made by any examiner of palmar or plantar keratoses, and the patient's daughter, a nurse, writes that there were never any warty lesions on the hands.

Case No. 18 (E. P., H. M. H. 27: 173): A sixty-one-year-old weaver was first seen in February 1927. Ten or eleven years before entry his physician had given him nine drops of Fowler's solution daily over a period of six months, for psoriasis. At entry, he had three reddish, slightly scaling, somewhat raised, and irregularly shaped patches on the back, each about 5 cm. in diameter, beside many smaller ones. There was a similar patch in the temporal region, measuring 1.5 cm. in diameter, which was ulcerated. The palms and soles were free of keratoses, but in spite of this a dermatological consultant diagnosed the lesions as being typical of arsenical keratoses. Radium was applied to six areas, and at subsequent visits thirteen additional areas were similarly treated. In 1931, the patient received a course of neosalvarsan and bismuth at another hospital. He has now been in the South Sea Islands for three years and writes that he still has several areas of psoriasis on the body, but that except for some prostatic obstruction, he is quite well. He has never developed palmar or plantar keratoses.

Case No. 19 (E. M., H. M. H. 27: 283): A fifty-three-year-old dentist was first seen in our clinic in March 1927. He had used Fowler's solution for a short time during his boyhood for pimples on the face. Examination showed one large, reddish, scaling area on the back, 3 x 4 cm. in size, with borders slightly elevated and pearly. Scattered over the back were several similar smaller lesions. The diagnosis of a dermatological consultant was "question of arsenical keratoses." The patient writes that at the present time there is a small ulcerated lesion above the right nipple which he will have treated soon. He has never had palmar nor plantar keratoses.

Age of Patients, Dosage, Length of Exposure

Only three of our fifteen cases were in women and all patients were forty-five or more years of age save one, who was thirty-seven.

It will be noted from an examination of the history of these patients that the exhibition of arsenic had, in most instances, preceded the appearance of the lesions by many years. Complete information on the dosages of arsenic and the length of time it had been taken could not be obtained, owing to the fallibility of memory after the lapse of so long a period. Five patients, however, stated that the arsenic had been taken from twenty-nine to forty years before admission to the hospital, and an additional five patients stated that they had taken arsenic from
thirteen to twenty-two years before entry. Two of these patients had continued their exposure to arsenic up to the time of admission. Two patients could recall no exposure to arsenic, one patient, eighty years old, was unable to give a history, and in two cases, in which death had already occurred, information in regard to arsenic had not been recorded. Only patchy information could be obtained relative to the amount of arsenic that had been taken by the patients; in some instances it had not been great.

FORM OF ARSENIC USED

Of the patients in whom a definite history of oral administration of arsenic was obtained, all had taken "a solution of arsenic," "a tonic," or "Fowler's solution. It is probably safe to assume that all were Fowler's solution, or possibly Donovan's solution, because of the almost universal use of these preparations for administering arsenic by mouth.

It appears that no organic arsenical can be incriminated as the cause of any of the lesions in our patients, save possibly in Case No. 13, and there only by conjecture. Three patients had received intravenous injections. In Cases No. 2 and No. 18, the appearance of the keratotic lesions had followed the use of arsenic and had antedated the intravenous injections. In Case No. 13 twenty intravenous injections of unknown composition had been given thirteen years before entry for "a run-down condition." Although the history suggests anti-ocular therapy, the patient denies syphilis by name and symptom, and states that his blood Wassermann was reported as negative just prior to the injections. Following the intravenous injections, he was given two intramuscular injections and took a medicine in drops for about eighteen months. His physician had been dead for about ten years at the time of the patient's admission, and all efforts to ascertain more accurately the nature of the drugs he received were of no avail. The fact should not be overlooked that this patient had been a weaver for thirty years, during a period when occupational arsenic poisoning from dyed textiles was not uncommon, especially from green fabrics which used often to be dyed with Schweinfurth green (15). Industrial legislation now protects weavers from this danger.

We have been able to discover but two case reports in the literature in which arsenical carcinoma and intravenous organic arsenicals were associated. A patient with arsenical keratoses and carcinoma reported by Levin (21) had received inorganic arsenic by mouth for psoriasis five years before he contracted the syphilis for which he received arsphenamine. Milch (25) reports a patient with an arsenical carcinoma of the heel to whom both Fowler's solution and neosalvarsan had been administered.

We have been able to find reports of three cases of arsenical keratoses without carcinoma which have followed intravenous injections of the organic arsenicals. Gauvain (12) reported a case of a man showing
slight keratotic lesions of the palms with pigmentation of the skin one year after having received six injections of arsphenamine. A second case, presented by MacLeod (22) as a case of arsphenaminic keratoses, was that of a girl of seven years who had had four injections of salvarsan. Hyperkeratoses were reported to have appeared with an acute dermatitis and to have subsided almost completely at the time of presentation one month after the last injection. It seems unlikely that this is a case of true keratoses. A third patient, a man of twenty-nine years, is reported by Timberlake (36) to have developed "hyperkeratoses of the nails of both hands and feet" eight years after eight injections of salvarsan.

The organic arsenicals have been used in the treatment of syphilis for several decades. Cacodylates have been used at least since 1896, atoxyl since 1905, and the arsphenamines since 1910. It appears significant that after so many years of the use of the organic arsenicals only very rare reports can be found in which they have been incriminated in the production of chronic arsenical lesions. The prediction of Ullmann in 1917 (37) that there would be a great increase in the numbers of arsenical carcinomas with the universal use of the organic arsenical compounds in syphilis, yaws, etc., has not yet been fulfilled. This may be due in part to the rapidity with which the organic arsenicals are excreted, with but little conversion to an active form, and in part to the short duration of the treatment. The opportunity for accumulation does not appear to be great.

Among the cases of arsenical keratoses and carcinomas reported in the literature as following ingestion of the drug medicinally, by the oral route, most have followed the taking of Fowler’s solution (potassium metarsenite [KOAsO]n, corresponding to 1 per cent of As2O3, flavored with tincture of lavender), Donovan’s solution (representing 1 per cent each of AsI3 and HgI2), or Asiatic pills (one part of As2O3 to 80 parts of black pepper), where the specific type of arsenic used is mentioned. These are all trivalent inorganic compounds.

Osborne (28), in describing the results of his microchemical studies on tissue removed from arsphenaminic keratoses, states: “In every instance the drug administered contained quintavalent arsenic, such as solution of potassium arsenite (Fowler’s solution) and solution of arsenous and mercuric iodide (Donovan’s solution), arsenic acid, sodium and iron cacodylate. None of the patients received trivalent arsenicals such as the various arsphenamines.” We presume that by “quintavalent” Osborne refers to the quinquivalent, i.e. the pentavalent, form of arsenic. But of the compounds he lists as “pentavalent,” only arsenic acid and the cacodylates are pentavalent; Fowler’s solution and Donovan’s solution, as previously stated, are both trivalent inorganic compounds. The arsphenamines are trivalent organic compounds. Since Osborne concluded that “arsenic in quintavalent compounds has a special affinity for structures of ectodermal origin” on the basis of an erroneous classification, a review of this work should be made with more accurate consideration of the chemical forms of arsenic dealt with.
Milch and McNeer have also subscribed to this classification by Osborne. McNeer (24) states that the "quintavalent" form is the type which produces keratoses and epitheliomas; yet, among the four cases he reports, two had received Fowler's solution, a third "a medicine chemically proven to contain arsenic" (reported previously by Haagensen as being Fowler's solution), and the fourth "arsenic therapy for anemia." All were presumably Fowler's solution containing trivalent inorganic arsenic. Milch (25) also refers to Fowler's and Donovan's solutions as "quintavalent" arsenicals, to the affinity of these compounds for ectodermal structures, and to their tendency to form keratoses. In the case of arsenical carcinoma which he reports, however, Fowler's solution and neosalvarsan, both trivalent arsenical compounds, had been given.

Two of our cases (No. 1 and No. 3) appear to be of occupational origin, from spraying fruit trees with arsenical sprays. These sprays are most commonly composed of Paris green (acetoarsenite of copper, Cu(C2H3O2)CuAsO₃) or liquid lead arsenate (usually a mixture of lead-hydrogen arsenate, PbHAsO₄, and basic arsenate, (AsO₄)₃H₂O). Possible methods of poisoning in these cases are by inhalation, by absorption through the skin, or by ingestion by means of contaminated hands or food. Two of our patients had been weavers by trade; in one of these, however, a definite history of medicinal exposure to arsenic was given. The exposure to arsenic in weaving has already been referred to.

TREATMENT

If the patient is still taking arsenic, this should, of course, be stopped; if the arsenic is of an occupational source, exposure should be avoided. Some patients may be found who will have had prescriptions for Fowler's solution refilled repeatedly without the knowledge of the physician who had originally prescribed the drug. Our Case No. 5 is an example of this.

Many of the keratotic lesions may be treated expectantly. Those which show any evidence of malignant degeneration should be destroyed by means of electrocoagulation, x-rays, or radium; some may require excision. All patients with lesions of the squamous-cell type should, in addition, have a block dissection of the lymph nodes to which the area is tributary, since two-thirds of the squamous lesions in this series which metastasized to lymph nodes did so in spite of a low histological grading.

An attempt has been made among our recent cases to stress the importance of systematic observation at intervals of from six to eight weeks. At these times all areas showing any evidence of early malignant changes are destroyed with radium, usually with a dose between 10 and 15 millicurie hours of unscreened radon directly applied. Often ten or more areas are treated at a visit. The areas of crusting keratoses on the body which cause discomfort by abrasion or by itching
after perspiration, are destroyed for prophylaxis and comfort, often with doses as low as 4 or 5 millicurie hours. Fissured hyperkeratoses on the palms and soles are likewise destroyed when they are at a site of continued irritation, especially over joints.

Sodium thiosulphate has been used by some clinicians with the expectation that it would hasten excretion of the arsenic stored in the skin. This compound is a relatively non-toxic reducing agent introduced by Ravaut (32) in the internal treatment of skin diseases of heavy metal origin, and later popularized in this country by McBride and Dennie (23). The theoretical object of its administration is to render the arsenic inert in the form of the non-toxic and insoluble sulphide and thereby remove the arsenic quantitatively from the body so far as further chemical action is concerned. This may operate in acute cases of arsenic poisoning, but when the arsenic has been resting in relatively avascular hyperkeratotic patches for periods up to forty years, it seems unlikely that it can be reached and mobilized, or rendered innocuous so simply.

The administration of sodium thiosulphate in Case No. 1 by Dr. William T. Salter, biochemist to the Collis P. Huntington Memorial Hospital, was not followed by any increase in the excretion of arsenic.

**DISCUSSION**

It seems timely that some admonition be sounded lest practitioners, unaware of the carcinogenic property of inorganic arsenic, inadvertently augment the growing number of individuals suffering from carcinoma of the skin. Most of our recent pharmacological textbooks fail to caution against its dangers, though Paris in his "Pharmacologiu" over a century ago summarized these aspects of arsenic very aptly when he wrote, "... the propriety and safety of its exhibition has been often questioned; there can be no doubt but that the greatest circumspection is required in the practitioner who administers it, and it ought not, in my opinion, to be employed until other remedies have failed; that it is capable of accumulating in the system is very evident, and this, in certain habits, may predispose the patient to serious diseases" (30).

With the obsolescence of its use in the anemias, Fowler's solution has had a recent surge of popularity in the treatment of other blood dyscrasias, in doses as large as 20 minims a day for several months at a time. The present study suggests that these cases must be followed for a number of years to ascertain whether carcinoma has not been substituted for a lesser evil.

Accounts of the mountaineering "arsenic eaters" of Styria, Hungary, and certain parts of Punjab are sometimes cited as evidence of the innocence of arsenic in the production of skin lesions; since it is said that these people, in spite of the ingestion of large doses of arsenic two or three times a week, live to old age with usually clear complexions. Critical investigators, however, have found that these people
invariably take the dry crystals of orpiment, composed chiefly of relatively insoluble $\text{As}_2\text{S}_3$; and it is thought that their supposed tolerance is based on this fact coupled with a possible acquired resistance of the alimentary tract to arsenic absorption, or a low kidney threshold (2, 39).

The ability of arsenic, by topical application, to produce carcinoma has been suggested by citation of the experimental production of a metastasizing squamous-cell carcinoma in mice by Leitch and Kennaway (20), after painting the skin with Fowler's solution. This, however, is unconvincing evidence, since this lesion was produced in only one of a hundred mice, and the caustic depilatory used, sodium sulphide, may have as appropriately been incriminated. Convincing evidence that arsenic is the cancerogenic agent in tar is wanting.

Arsenic has been a common constituent of quack cancer pastes, and an occasional patient is still seen who gives a history of arsenic paste treatment for his carcinoma. It is deplorable that statements such as the following may still be found in pharmacological books: "Locally arsenic is a valuable caustic for the destruction of malignant growths." For this purpose arsenic has no place.

Conclusions

1. Nine cases of carcinoma definitely due to arsenic and five cases of carcinoma probably of arsenical origin are reported. One case in which keratoses only were caused by arsenic is described. Four additional cases, illustrative of lesions possibly produced by arsenic, are discussed.

2. Arsenic may become deposited in the skin and manifest its carcinogenic property as late as forty years after the ingestion of, or occupational exposure to, arsenic.

3. The carcinogenic property of inorganic arsenic is not universally appreciated, and, as a result, cases of carcinoma of the skin may inadvertently be produced.

4. Inorganic trivalent arsenic, usually in the form of Fowler's solution, appears to be the chief offending agent.

5. Chronic arsenical lesions following the administration of organic arsenical compounds are exceedingly rare.

6. That arsenical carcinomas are not invariably of the squamous-cell type is evidenced by the fact that more than one-third of the carcinomas in this series were of the basal-cell type.

7. Although the grade of malignancy in the squamous-cell lesions is usually low, metastasis to groin and axilla is not an infrequent event, as attested in our series by this occurrence in 9 lesions, two-thirds of which were graded I, histologically. With all lesions of any considerable size, therefore, the regional lymph nodes should be removed, in spite of a low histological grading.

8. Patients with early arsenical lesions may be spared extensive operations or untimely death by prophylactic destruction of precan-
cerous arsenical keratoses; or by careful and frequent observation, these keratoses may be destroyed at the moment malignant changes threaten.

BIBLIOGRAPHY