PC B - Japan

Comment

CHLORACNE

A significant milestone has just been passed in the understanding of this condition.

Although chloracne has been established as a recognizable and distinct entity for nearly 80 years, it was not until the publication of a Japanese monograph in June, 1969 (Katsuki et al., 1969) that it became an established fact that the disease could be caused in the human subject by the internal administration of a substance known to be capable of inducing chloracne by external contact, the route by which the vast majority of cases have been produced in industry in years gone by. Whenever systemic absorption had been suspected in the past, with one notable exception, gross external contact had also been present. Since the subject has been extensively reviewed by Crow (1970) this review will be confined to the Japanese monograph.

The discovery, resulting from a very fine epidemiological investigation, that severe chloracne occurring among family units in Fukuoka province had resulted from the ingestion of tetrachlorbiphenyl was all the more notable because of the impossibility of producing the picture of chloracne in experimental animals by oral administration of chloracne-producing substances, whilst the use of human volunteers is impossible.

It is true that follicular hyperkeratosis has been reported experimentally (Rimington and Ziegler, 1963) and a histological picture at least resembling chloracne was produced by the so-called "X disease" of cattle caused by the accidental ingestion of chloronaphthalenes in the 1940's and 1950's (Wagner, 1951), but never the clinical condition of chloracne as we know it in the human subject.

The recent poisoning in Japan resulted from the contamination of a cooking oil, during the manufacture of which tetrachlorbiphenyl was used as a heat exchange medium whence it escaped undetected into the edible oil which contained an average of 2000 p.p.m. of the chlorbiphenyl. Most patients probably ingested 4–5 G. during the course of 5–6 months, but these figures are very approximate because the escape was intermittent (Calnan, 1970). When the fault was finally discovered and remedied further cases ceased to appear. Of several hundred patients 138 were closely studied in the Department of Dermatology at Kyushu University.

Apart from fatigue, malaise, nausea and anorexia the commonest presenting signs were firstly, cystic swelling and hypersecretion of the meibomian glands, which became swollen and discharged a creamy, cheese-like substance, with oedema of the eyelids and, secondly, chloracne. These physical signs usually appeared within 2 months of ingestion. The chloracne was typical, consisting of a mixture of comedones and straw-coloured cysts varying in size from a pin head to a pea. In 20 cases inflammatory papules and pustules were also present. Just as in 6 other cases of chloracne from ingestion of an unknown chlorinated hydrocarbon (Crow, 1970) the worst affected areas were, in order of frequency, the head, neck, genitalia, and trunk, especially the upper half. The forearms were rarely affected and the lower limbs scarcely at all. One interesting finding was a widespread follicular hyperkeratosis, mainly on the trunk in the more severe cases, a change which has been reported previously only 3 times in association with human chloracne (Crow, 1970). It is of interest that so far, 2 years after the onset of poisoning, the chloracne is largely unchanged (Calnan, 1970).

There were many other abnormalities in established cases, but by far the most striking was melanin hyperpigmentation, most marked on the fingers, toes and nails—which were often flattened—in the milder cases, whilst in the most severe it was generalized. It affected the conjunctivae, gums and lips in a high proportion and was the presenting sign in 13 cases. Two other rare findings were enlargement of Montgomery's glands of the breasts and localized hyperkeratosis of the palms and soles.

Other cutaneous findings concerned the infants born to women with the established disease. They all exhibited generalized desquamation and hyperpigmentation of the

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skin and excessive pigment in the gums and nails. These changes disappeared and the infants were normal within a few months. No other abnormalities were observed in the neonates, 2 of whom were still-born.

Some of the non-dermatological features of intoxication were among the most interesting. Oedema of the face was relatively common in severe cases, but in a few was accompanied by oedema of all 4 limbs. Dysmenorrhoea and decreased potency were common enough to be of almost certain significance. Arthralgia and joint swelling were rare, as was a remarkable ulnar and prepatellar bursitis, a finding which has been reported only once previously—namely in cases of poisoning from pentachlorphenol (Baader and Bauer, 1951). This same report details the only previously recorded suggestion of neuropathy in association with chloracne, and it is of great interest that, in 23 Japanese cases of tetrachlorbiphenyl poisoning who underwent thorough neurological investigations, no less than 10 had symptoms of sensory neuropathy such as numbness, pain and hypoaesthesia, whilst sensory nerve conduction velocity was slowed in the radial and sural nerves of 9 cases.

Probably the most important finding to emerge from the entire study was also the most consistent. No less than two-thirds of all patients had a marked hyperlipidaemia, the increase being confined to the triglyceride fraction. Secondary xanthomata were not described. That this finding was specific was further confirmed by animal experiments on rabbits—of less significance in view of this animal's great susceptibility to this change—but most significantly on rats whose serum triglycerides were increased more than 10 times over the control animals. Such findings had been mentioned once previously, almost in passing, when describing severe poisoning from 2,4,5 trichlorophenol, with gross chloracne (Crow, 1970), but the Japanese cases of tetrachlorbiphenyl poisoning are compared with the more severe hypertriglyceridaemia recorded in the same monograph by Goto in 10 cases of poisoning from pentachlorphenol. Evidence of liver damage was minimal in the patients poisoned with tetrachlorbiphenyl.

Finally, attempts were made to reproduce the skin changes experimentally; hairless mice were fed 4 G. of the contaminated cooking oil per week for 10 weeks, i.e. an approximate total dose of 80 mg. of tetrachlorbiphenyl. After 7 weeks there was hyperkeratosis of the lower abdominal wall which then extended to other areas of the skin. The liver was enlarged and showed fatty degeneration. Histologically the skin showed marked cystic dilatation and hyperkeratosis of the hair follicles, changes identical to those of the cattle poisoned with chlornaphthalenes. Controls were normal. This does at least strengthen much further the presumption that chemicals producing these changes after ingestion by experimental animals are likely to produce chloracne in the human subject.

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