SWINDON AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE

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22nd February, 1972

Mr. M. Thompson,
Technical Fluids Manager,
Monsanto Chemicals Ltd.,
10-18 Victoria Street,
London SW1H CNO.

RECEIVED

Dear Mr. Thompson,

I have recently been in correspondence with Dr. Newman and another of your colleagues once again, this time concerning Chlorophenols and, owing to loss of records - and loss of memory!. - I had a horrible feeling that I might not have sent you a reprint of my Dowling Oration on Chloracne in the preparation of which you gave me much useful advice, which I have acknowledged.

In case I failed to send one I enclose it herewith.

With kind regards,

Yours sincerely,

K.D. Crow, F.R.C.P.,
CONSULTANT DERMATOLOGIST.

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To Mr. Michael Thompson, Technical fluids Manager.

CHLORACNE†

A CRITICAL REVIEW INCLUDING A COMPARISON OF TWO SERIES OF CASES OF ACNE FROM CHLORNAPHTHALENE AND PITCH FUMES.

K. D. CROW‡

A review of the subject of chloracne will be followed by a comparison of the manufacturing processes and cases produced during two factory outbreaks of chloracne and pitch acne both due to fume exposure.

My definition of chloracne is the production in the human subject of a type of acne with characteristic clinical features, so far produced only by aromatic chlorinated hydrocarbons of varying structure. Acne caused by paraffins, whether chlorinated or not, is clinically distinct from chloracne and all such cases should be regarded as oil acne. Acne due to pitch and heavy coal tar distillates is also usually distinctive.

Chloracne has previously been reviewed only once by Braun in a German monograph in 1955[7]. This was essentially bibliographical apart from its report of the author's own work. Moreover, there have since then been some important developments in our understanding of this condition.

It also seems unlikely that we shall ever again see the thousands of cases of chloracne which occurred in the 1930's and 40's, and since there may be some of us today who have never encountered this now uncommon industrial disease a reminder of its characteristics may be of value.

It is unnecessary to make more than the briefest mention of the early history of this condition, for in most cases the chemistry involved was known only vaguely if at all, and the great value of the early works was their recognition that the acne they were observing was clinically distinct from that due to products of coal tar and paraffinnic oils. First Von Bettman[3] in 1897, and then Herxheimer[37] observed this distinctive acne among workers engaged in the manufacture of hydrochloric acid by the old method using tar lined absorption towers and the newer electrolytic method using anodes of tar, bitumen and charcoal. Only workers exposed to the tar were affected.

Although Herxheimer at first blamed nascent chlorine—hence the term chloracne—he soon agreed that chlorinated aromatic hydrocarbons were the most likely cause. For many years some authors clung stubbornly to the nascent chlorine theory and even suggested that the chlorine in chloronaphthalenes was easily released to do its deadly work[73,74,75], whereas in fact it was the very converse which made them such useful industrial materials! It was of course suggested that all the cases described as chloracne were in fact tar acne and that chlorination had nothing to do with it at all[59], but these early observers[46] were familiar with coal tar acne, and their descriptions of chloracne, in particular the emphasis on the peculiar cyst-like lesions[37] leaves little doubt that they had correctly distinguished between the two conditions.

The substances which I shall now consider in detail are Chlornaphthalenes, Chlordiphenyls and Terphenyls, Chlordiphenyl Ethers, Furanes and Dioxanes, Chlorophenols and Chlorobenzenes (fig. 1).

CHLORNAPHTHALENES

The production by the chlorination of naphthalene of numerous isomers with wax-like qualities was first noted by Laurant in 1883[80], but it was not until 1900 that J. W. Aylsworth in the U.S.A. took out several patents after noting some of the

†The Dowling Oration, delivered at St. Thomas' Hospital on Friday, 17th April, 1970.

‡Princess Margaret Hospital, Swindon, Wilts.

With compliments

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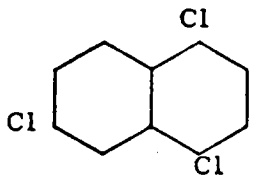
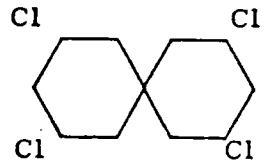
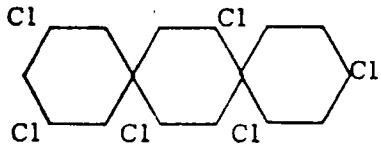


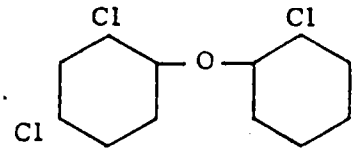
Trichlornaphthalene



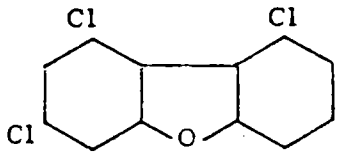
Tetrachlordiphenyl



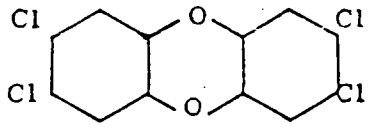
Hexachlorterphenyl



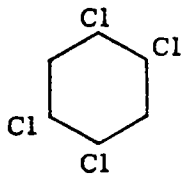
Trichlordiphenylether



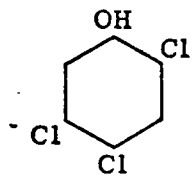
Trichlordiphenyl(ene) oxide
or Trichlordibenzofurane



Tetrachlordibenzodioxane



Tetrachlorbenzene



Trichlorophenol

Fig. 1.—Representative formulae of some substances discussed in the text.

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remarkable properties of these materials, i.e. clinical inertness, high dielectric constant, low viscosity close to the melting point, low shrinkage, non-inflammability, fungicidal and insecticidal properties and strong adhesion to various surfaces including metal. Their use by the Germans in World War I as substitutes for natural waxes and rubber led to the first large outbreaks of chloracne. Partly for this reason and due also to the post-war reappearance of traditional materials there was a great decline in their use until the mid 1930's, when their great superiority to paraffin wax brought them to the notice of capacitor (electrical condenser) and cable manufacturers[44,12,26,13]. Large scale usage recommenced and with it great outbreaks of chloracne. Their industrial applications rapidly widened to include numerous other uses ; as synthetic waxes[55] and impregnants; high pressure additives for lubricants[33,68]; wood preservatives[82] ; flame proofers and many functions now superceded by silicones and plastics[61,78].

MANUFACTURE

The method of manufacture is simple ; it is achieved by the direct, continuous chlorination of molten naphthalene under high pressure which results in a mixture of chlornaphthalenes from alpha monochlor- to octochlor-. The commercial products are distilled and graded simply according to their chlorine content and all are therefore mixtures of various isomers with one or two main derivatives predominating. Some typical examples of Halowax(R)* chlornaphthalenes are shown in Fig. 2.

The ability of all chloracne producing substances to induce chloracne depends upon two things ; their physical state and the degree of chlorination.

PHYSICAL STATE

From the physical standpoint chlornaphthalene fumes are far the most potent ; solutions less so, and contact with the solid substance of little importance except under special conditions.

The fumes from molten chlornaphthalenes are in fact a sublimate, and become profuse at temperatures far below the boiling point. When acneigenic this is the property which makes them difficult to use safely in industry. Their ability to condense on cold surfaces[81] may cause them to accumulate in the ducts of ventilating systems, thus reducing their efficiency. Solutions may well be less troublesome because it is easier to avoid skin contact but again chloracne is frequent[30]. Although it has often been stated that the solid wax in macroscopic particles causes severe chloracne, in every such publication there has either been exposure to fumes from a nearby process[49] or a simple failure to appreciate their appearance in the process being considered. Thus Schwartz in 1943[65] described chloracne from solid particles among shipyard cable strippers but in the very same article he mentions their exposure to fumes, and it is known that these workers habitually melted the waxes to seal the cable ends and joints and were indeed fume exposed[27,41]. On the other hand prolonged contact plus friction may be significant, and a German child whose feather mattress was annually rubbed all over with a chlornaphthalene cobblers wax to prevent escape of feathers, produced chloracne on his cheeks and the sides of his arms and legs[38]. This cleared up when the mattress was destroyed. The same authors state that they had observed chloracne in leather and tent factories, which disappeared when a synthetic chlornaphthalene wax was abandoned in favour of a return to the traditional bees-wax. These latter cases, occurring only three years ago, serve as a warning that, although the higher chlorinated naphthalenes are little used in industry today we may still come across them from time to time under certain circumstances.

Occasionally workers, usually of dirty habits, may produce chloracne in the

*(R) Trade Mark of Koppers Co. Inc., Pittsburg 19, U.S.A.

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same way in their children whom they cuddle on return from work and also in their wives[26,67].

So much then for the physical state : even more important is the degree of chlorination.

DEGREE OF CHLORINATION

Until 1957 there was general agreement among all authors that as the degree of chlorination increased so did the systemic toxicity and the acneigenic properties of chlornaphthalenes. As a result of Shelley and Kligman's[69] experiments on human volunteers, the unexpected fact emerged that whereas tri and tetra, hepta and octachlornaphthalenes were entirely non-acneigenic, the penta and hexachlor derivatives produced very severe chloracne indeed. Since Shelley deliberately chose suspensions

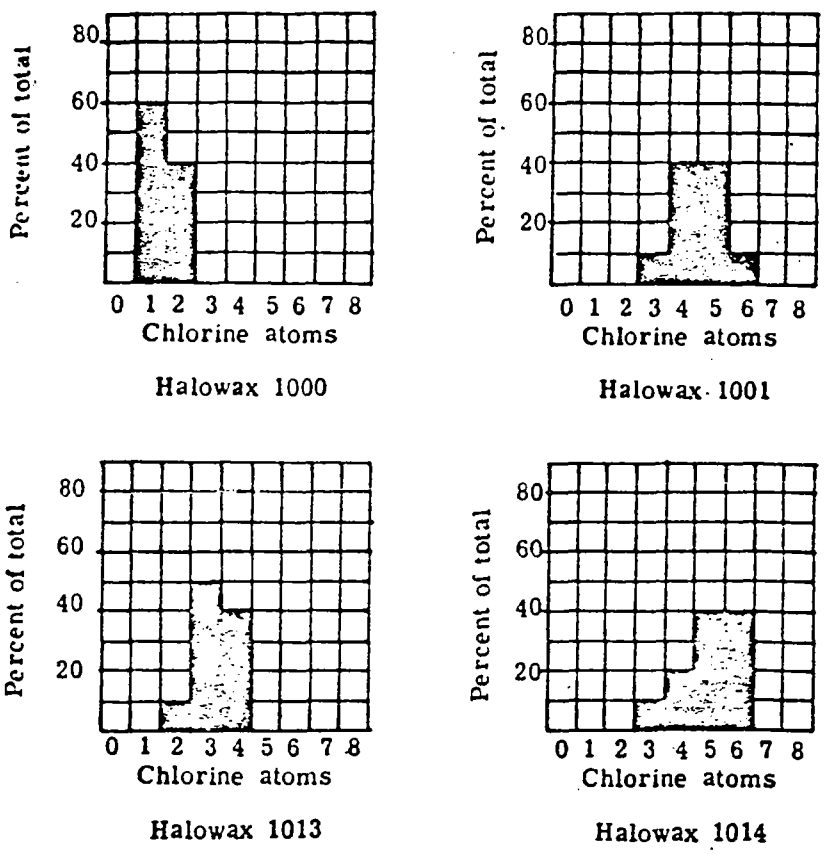

FIG. 2.—Examples of four Halowax chlornapthalenes.

of fine particles rather than solutions, varying solvents and solubilities cannot have accounted for the surprising failure of the two most highly chlorinated derivatives to have any acneigenic effect. Hambrick[35] in 1957 employing the extremely sensitive experimental technique described in 1941 by Adams et al[1] using the inner side of the rabbit ear, had already demonstrated that mono- and di-chlornaphthalenes did not produce chloracne, thus clearly incriminating only the penta- and hexachlor derivatives. This work is strongly confirmed by the massive outbreaks of chloracne

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which occurred during the late 1930's and 40's largely in the manufacture and use of electric cables[13,27,30,49] whose outer covering was a fabric impregnated with penta and hexachlornaphthalene. It therefore seemed clear that the assumption of steadily increasing toxicity with increased chlorination had been based on insufficient evidence. Animal experiments on systemic toxicity had paralleled the acneigenic effects but hepta and octachlornaphthalene had never been tested in this respect, a fact now most difficult to understand. There is no reason to dispute the fact that mono and dichlor, hepta and octochlornaphthalenes are non-acneigenic but the position with regard to tri and tetrachlornaphthalenes, which invariably exist as a mixture, is more confusing. Several reports of chloracne from trichlornaphthalene used as a paper capacitor impregnant appeared in the French and Belgian literature in the early 1930's but they do not stand up well to critical analysis. Although the information is incomplete in many respects there are various reasons for believing that other factors were probably responsible for the acne in these cases. It is, for instance, well known that molten pitch was extensively used at that time to seal capacitors after impregnation[71], and was also mixed with the trichlornaphthalene itself in certain cases[14]. It therefore seems likely that pitch was at fault, a suggestion strongly supported by Duvoir[24]. It is even possible that pitch may have conferred upon the mixture acneigenic properties not possessed by tri and tetrachlornaphthalenes alone. The presence in some of these cases of a co-existent vesicular dermatitis on the face[14,49], and in others of a photosensitivity[32], the description of which was identical to that of pitch smarts[17], is probably relevant. This is further confirmed by the fact that, since pitch has disappeared from capacitor manufacture, so have reports of acne, dermatitis, and photosensitivity from tri and tetrachlornaphthalene, although these substances have continued to be used extensively for paper impregnation. Furthermore, the subsequent observation of vast numbers of workers exposed to various chlornaphthalenes only, has produced no further evidence of contact dermatitis. A report by Nakauchi[34] describing two cases of chloracne in a capacitor plant using a tri/tetrachlornaphthalene wax for impregnation is valueless in the absence of details of the chemistry or process of impregnation or, more important, of sealing. On the other hand, the same author, although providing no experimental data at all, exposed rabbit ears to the vapour of trichlornaphthalene for several months and noted the development of comedone-like keratoses and hyperkeratosis. Assuming that the chemistry was correctly reported such gross exposure of the very highly sensitive rabbit ear may represent conditions which are not capable of extrapolation to the human situation.

Certainly my own work confirms my opinion that there is no evidence that tri/tetra chlornaphthalene mixtures are acneigenic or dermatitic under industrial conditions.

PRESENT USES

I think it is important to know the present uses of chlornaphthalenes in Great Britain.

All major manufacturers of these products either ceased production altogether several years ago and handed over to smaller firms, or make a range of products which does not include chlornaphthalenes with more than four chlorine atoms per molecule. Extensive enquiries in the United Kingdom lead me to believe that these materials are at present used here for paper capacitor impregnation, only as tri and tetrachlornaphthalene and on an increasingly small scale; also in timber preservatives as mono, di, tri and tetrachlor derivatives. Nevertheless, the higher chlorinated products are still manufactured abroad and therefore are available, so that the possibility of their presence must always be suspected in chloracne of unknown origin. When I recently examined capacitor impregnation processes using tri/tetrachlornaphthalene mixtures once again I found no evidence of chloracne.

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CHLORDIPHENYLS AND TERPHENYLS

Whilst the uses of chlornaphthalenes are contracting so the applications of chlordiphenyls in modern technology are constantly expanding.

They are produced, like the chlorinated naphthalenes, by the direct chlorination of molten diphenyl and, like chlornaphthalenes, are mixtures of isomers usually with one material predominating. They were little used until about 1930 when the Westinghouse Company discovered their great advantage over mineral oils in the manufacture of high voltage paper capacitors and as transformer oils.

They vary from colourless mobile liquids (the monochlor) through ever thicker oily fluids to an off white powder—octochlordiphenyl. The chlorterphenyls are usually resinous solids and there are also numerous mixtures of chlorinated diphenyls and terphenyls, most of which again exist as low melting point thermoplastic resinous substances.

Chlordiphenyls resemble the chlornaphthalenes in their great chemical inertness and resistence to oxidation, non-inflammability, flame proofing qualities and a very high dielectric constant i.e. insulating ability. These qualities, together with the fact that liquids, unlike waxes, do not form voids or spaces when impregnating paper, made them seem ideal materials for paper capacitor impregnation especially for voltages over 250 A.C. but they are great ionic solvents, unfortunately the more so as their chlorine content decreases and the dielectric value correspondingly rises. The great problem here lies in the fact that not only traces of moisture but also the minutest ionic contamination is fatal to capacitor functioning. The major difficulty was to produce strong, thin Kraft papers which were ionically pure. Eventually these problems were solved and large scale manufacture of chlordiphenyl capacitors began in Britain around 1950. Pentachlor-diphenyl was first used for this purpose but it had the serious draw-back of being unusable at temperatures below 0°C when it solidified and for low temperature A.C. use paraffins continued to be used. Finally the ionic difficulties of using the greatly superior trichlordiphenyl as a high voltage capacitor impregnant were overcome and its use is now almost universal. Because the capacitor industry is the country's largest user of chlordiphenyls I have disucussed it at some length. As the number of available compounds has increased, their uses have multiplied constantly until today there are well over 100 different industrial applications for polychlorinated diphenyls and terphenyls[53]. A detailed analysis is therefore quite beyond the scope of this article but their uses stem essentially from their three major properties ; resistance to oxidation, non-inflammability, and high dielectric value. I shall mention one specific use because it has been the cause of the only two outbreaks of chloracne from these materials published since the 1940's. This is their function as heat transfer agents in chemical engineering[42,50]. Previous chloracne had resulted from crude and careless manufacture in the early days[43] or admixture with chlornaphthalenes.

TOXICOLOGY

Once again, as in the case of chlornaphthalenes, their acneigenic potential is similarly dependent upon their physical state and the degree of chlorination. The published work on the toxicology of the chlorinated polyphenyls is small, due largely to the lesser problems posed by their industrial uses. Nevertheless their toxicity to experimental animals is greater with an increasing number of chlorine atoms certainly up to 7. Thus Miller's rats[52] all survived over 60 days after receiving ten 0.5 ml doses of trichlordiphenyl on alternate days, whereas Drinker et al.[18] killed 50% of their rats with the same dosage of heptachlordiphenyl in less than 14 doses.

Unlike the chlornaphthalenes they do not sublime at low temperatures whilst at moderate working temperatures fuming is slight and when cold entirely absent. Relatively mild fume exposure in the capacitor industry caused occasional chloracne

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with pentachlordiphenyls[60] although this was not to be compared with that from penta and hexachlornaphthalene. Since the change to trichlordiphenyl however even this has entirely disappeared[39], as I can confirm from my own recent inspection of some two thirds of the British capacitor industry which was using this material extensively. Contact with the cold liquid chlordiphenyls, although undesirable because of skin absorption, appears to pose no acneigenic hazard.

The lesser toxicity is confirmed by the entire absence in the literature of any reports of chloracne from chlordiphenyls containing less than four chlorine atoms. Furthermore, as will be seen in a later section of this paper, although these substances are hepatotoxic, this effect also seems to be minimal with only four or less chlorine atoms per molecule as the human ingestion of tetrachlordiphenyl in Japan has well illustrated.

CHLORDIPHENYL OXIDES

Experiments have been made with chlordiphenyl oxides or, more correctly, the dibenzofuranes as possible alternatives to chlordiphenyls. There is some confusion in the literature between these compounds and the true ethers of chlordiphenyls. The distinction is most important for the ethers[64], like all such compounds whether aromatic or aliphatic, are relatively inert even when chlorinated, whereas the furanes are chemically and biologically much more active. The chemical differences are clearly shown in fig. 1. The systemic toxicity and acneigenic properties of the chlordibenzofuranes or chlordiphenyl-oxides caused industry to abandon them and the question is now largely academic.

CHLOROPHENOLS

The study of the chlorinated phenols is probably the most fascinating aspect of the entire subject of chloracne because of its complexity. They range from mono to pentachlorophenol with, of course, various isomers of the lesser chlorinated compounds. They are used almost exlusively as insecticides, fungicides and herbicides, or as chemical intermediates. Consequently they may contact the human subject either during their use or their chemical manufacture. They are prepared by the alkaline hydrolysis of crude chlorobenzene, one chlorine atom of which is replaced by the hydroxyl group. Because of impurities in the basic chlorobenzenes any single chemical product will contain other chlorophenols and reaction products, the latter varying according to temperature, pressure and other variations in the chemical processes in use. These variations, as we shall see later, may be of significance as far as acneigenic potential and systemic toxicity are concerned. Their direct irritant effects upon the skin and mucosa are variable for each compound and also depend upon their physical state. In very dilute solutions their systemic toxicity is severe[28,51], whereas they have little cutaneous effect beyond that of the solvent ; but in strong solutions they can be not only toxic but also powerful skin irritants. In finely powdered form, especially when highly chlorinated, they are extremely irritating especially to the eyes and upper respiratory tract, and it is in this state that they have produced most of their chloracne. Indeed in large plants manufacturing various chlorinated polyphenyls and chlorophenols today it is the fine dust of the latter which is the main chloracne producer if it is not most carefully controlled[56]. It is therefore not surprising that in 1937 Butler[10] reported extremely severe and generalised chloracne in men shovelling a fine powder of sodium tetrachlorphenate and ortho (2 chlorophenyl)-phenol sodium into sacks under bad working conditions, again as a timber preservative. Large numbers of very severe cases from sodium tetrachlorophenate solutions used as timber preservatives were reported by Stingily and Gaines in 1940[70] but no details of strengths or solvents were given. Curious features of this and similar outbreaks were the grossly irritant nature of the solutions with the production of bullae and ulcers but the chloracne was apparently typical. Around 1950 the more effective pentachlorophenol replaced the lower chlorinated derivatives as a wood preservative.

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Chloracne from pentachlorophenol solutions has never been recorded despite gross skin contamination. Nevertheless fine dusts have continued to produce it always in the manufacturing plants. Baader and Bauer in 1957[2] reported an outbreak of particular interest because of the association with peripheral neuropathy and olecranon bursitis. Plant conditions were evidently bad, for severe irritation of the eyes, nose and respiratory tract were universal thus implying considerable airborne contamination with finely powdered material[58].

Kimmig and Schulz in 1957[45], faced with a severe outbreak of chloracne in a chemical plant manufacturing 2, 4, 5-trichlorophenol and using the technique described by Adams et al. in 1941[1], quickly established for the first time the vital but elementary fact that whereas the plant's crude trichlorophenol had an acneigenic effect on the inner side of the rabbit ear painted with 5% solutions in polyglycols, neither the intial reaction product crude 1, 2, 4, 5-tetrachlorobenzene nor purified 2, 4, 5-trichlorophenol, did so even in 10% dilutions.

It was therefore assumed that a reaction product of the alkaline hydrolysis of the chlorobenzene to trichlorophenol might be responsible. The residues in the reaction vessels and pipe-work of the plant were so complex as to defy analysis, and so for two years they proceeded to test on the rabbit ear over 100 substances which might theoretically form under the conditions of manufacture. Many interesting facts gradually emerged. Neither true diphenyl ethers nor their chlorinated derivatives were acneigenic or toxic, whereas chlordiphenyl oxides or, more correctly, chlordibenzofuranes were potent acneigens even in 0.05% solutions, and also highly hepatotoxic, a single dose of 0.5 to 1.0 mgms per kgm. of trichlorodibenzofurane being lethal to rabbits. Finally they found a substance so potent that 0.001% solutions were strongly acneigenic[47]. This material was the chlorinated dibenzyl cyclic ether, tetrachlordibenzodioxane. Its systemic hepato-toxicity paralleled its acneigenicity and 0.05 mgms in a single dose was lethal to rabbits.

Although the position of the chlorine atoms was not absolutely certain[64], what was thought to be 2, 3, 6, 7-tetrachlordibenzodioxane was isolated by Kimmig from the residues resulting from the formation of trichlorophenol by the alkaline hydrolysis of tetrachlorobenzol, and its theoretical formation was postulated as shown in fig. 3.

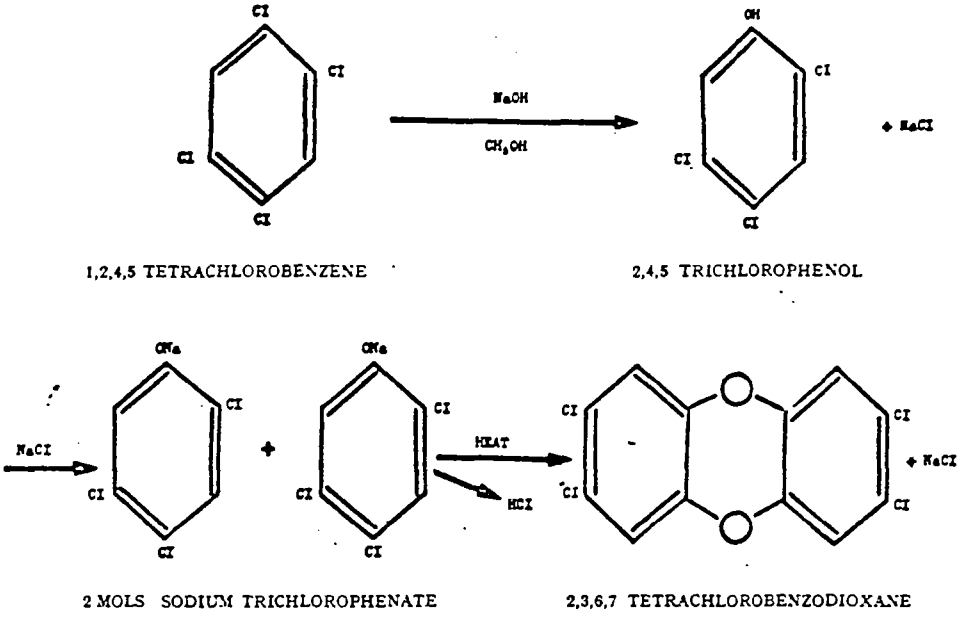

FIG. 3.—Stages in formation of 2, 3, 6, 7-tetrachlordibenzodioxane

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The presence of erythema and swelling of the face and chronic blepharo-conjunctivitis all suggested exposure to fine chlorophenol dust, and when this was rectified the chloracne ceased.

Kimmig suggests that, if not tetrachlordibenzodioxane itself, then substances closely related to it are probably responsible for chloracne, not only from trichlorophenols, but possibly tetra and pentachlorophenols also, all of which are similarly produced by alkaline hydrolysis and heat from the relevant crude chlorobenzenes.

The great importance of this classic work lay in its emphasis on the basic necessity of establishing whether or not a suspected substance is still toxic when highly purified.

At the same time also in a trichlorophenol plant, Dugois and Colomb in two identical articles[20] described chloracne of great severity and with evidence of systemic toxicity in a number of workers who, without protective clothing, were washing out with hot water the accumulated sodium chloride in the reaction vessels. Twelve years later in the very same factory Dugois, again in two identical articles[19], described an apparently unique outbreak of chloracne from a single exposure, of only a few hours duration, to residues released by an explosion of the pipe work. Explosions suggest increased pressure and possibly heat, factors both increasing the chance of dibenzodioxane formation. Chloracne in these cases, just as in Kimmig's, was preceeded by erythema and oedema of the face.

Although Dugois' paper was short and without detail or explanation it mentions the isolation of a tetrachlorated ether oxide, a chemically meaningless term, but one is left wondering whether they had in fact isolated the tetrachlordibenzodioxane described by Kimmig eleven years before. Chloracne from a single exposure to any material is so unusual that one cannot exclude systemic absorption as Dugois suggested, especially as malaise, anorexia, loss of weight and milky serum with raised cholesterol and fat were also mentioned briefly. Nevertheless one cannot possibly agree with Dugois in ruling out external contact, since Linn-Jones and Krizek[47] produced acne on the rabbit ear with only three paintings of a 0.001% solution of tetrachlordibenzodioxane.

In 1964 Bleiberg[5] linked for the first time chloracne and hepatic porphyria, again in a plant manufacturing dichloro and trichlorophenols for conversion to the relevant phenoxyacetic acid weed killers.

In my opinion it is of the greatest significance that there was no direct relationship between the chloracne and the porphyria, some cases having one condition without the other. This unique occurrence required an investigation of the same calibre as Kimmig's but unfortunately the industrial and chemical information was incomplete and sometimes incorrect. Nevertheless whilst prophyria from chlorophenols clinically or experimentally has never been recorded[48] there is abundant evidence of its production both clinically and experimentally from chlorobenzene isomers of many different kinds[62]. Therefore there seems little reason to doubt that the chloracne was probably produced by chlorodibenzodioxanes or similar substances as Kimmig and Schulz had already demonstrated, whilst the porphyria was most likely induced by the crude chlorobenzenes used to produce the chlorophenols.

CHLOROBENZENES

What evidence is there that chlorobenzenes themselves cause chloracne ? In fact, very little. Exposure to various chlorobenzene isomers has occurred on a vast scale over the years both externally and internally in human subjects[63] and experimental animals without causing chloracne.

The only cases reported in human subjects were in men who were grossly exposed to the fine dust and vapour of crude trichlor and hexachlorobenzenes, producing a few rather atypical looking cases of chloracne which ceased when the process was extracted. This report by Bowen and Moursund[6] was lacking in chemical and engineering

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detail and in view of the complexity of the reaction products in such chemical manufacturing plants this interesting report requires further confirmation.

On the experimental side Rimington and Zeigler[62], feeding rats numerous chlorobenzene isomers, found that only 1, 2, 3, 4-tetrachlorobenzene produced patchy hair loss, keratotic plugging of the follicles and disappearance of sebaceous glands, these changes resembling those of chloracne. The other chlorobenzenes tested including 1, 2, 4, 5-tetrachlorobenzene were without effect. All this rather suggests that chloracne may be produced only by certain chlorobenzenes, and indeed even by one isomer and not another. Further research is clearly indicated.

There have been reports, mostly very old[7], of chloracne from other materials, but none of these stand up to critical analysis.

RATE OF ABSORPTION AND SYSTEMIC TOXICITY

Now we accept that chloracne is caused by exposure to certain chemicals but a vital question remains ; are the effects purely external, secondary only to systemic absorption, or a mixture of both ?

There can be little doubt that the vast majority of cases produced by industry have been due to external contact alone, especially when only one side of the body has been involved[11]. Furthermore where undoubted systemic effects have occurred there has been gross external contact also[2,20,23,29]. There was always a doubt therefore whether internal administration could cause chloracne at all, and if so what part it played in any particular case.

The first concrete evidence appeared in 1945, when a fat-like substance found in the bomb ruins of Berlin was used to fry vegetables and six people were poisoned[36,76]. There were no deaths and apart from general symptoms, mainly gastrointestinal, first redness and oedema, and then severe chloracne appeared, involving only the face and neck in three cases, the chest and back also in three others, an interesting observation indicating that distribution in itself does not allow one to distinguish between external and internal causation. Such analytical data as were available suggest that they had probably ingested hexachlornaphthalene, but the identity of the poison has always been the subject of some doubt. Further support was provided by the eventual discovery that the mysterious "X disease"[57], a fatal wasting sickness with hyperkeratosis and dilatation of follicles which had decimated cattle in the U.S.A. and Germany from 1941-1954, was due to the accidental ingestion by them of penta and hexachlornaphthalenes in lubricating oils and greases[83] and timber preservatives[79]. So sensitive were cattle that a single oral dose of 1.0 gram of hexachlornaphthalene would kill a 2 cwt. calf in 14 days[4].

The final conclusive proof that chloracne can result from systemic intoxication of the human subject with no external contact at all came from Japan in June 1969 ([42]).

This was the report of an outbreak of poisoning due to tetrachlordiphenyl which, for three days only, leaked from the heat exchange system in a factory manufacturing cooking oil. The edible oil contained an average of 2,000 p.p.m. of tetrachlordiphenyl and most patients probably took something like 1.0 gram per month for 4-5 months. Apart from fatigue, malaise, and nausea the earliest visible findings were ophthalmic with swelling of the eyelids and discharge, due to increased activity and cystic swelling of meibomian glands. 113 of 138 cases developed chloracne, which began slowly two months later and developed relentlessly for several months more.

As in Hertzberg's cases the chloracne was most severe on the face and neck but also the genitalia, though less so on the trunk and scarcely at all on the limbs. In the more severe cases there was often a widespread follicular hyperkeratosis also observed by Duverne[23] from trichlorophenol derivatives and from chlornaphthalenes by Hofs[38] and Braun[8].

The other most distinctive feature of the Japanese cases was a generalised pigmentation of the skin affecting also the lips, gums and nails. Also observed was enlargement of Montgomery's glands, and hyperkeratosis of palms and soles. Perhaps

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most interesting of all were some non-dermatological findings such as oedema of all four limbs, peripheral neuropathy and bursitis—also reported by Baader and Bauer from pentachlorophenol poisoning—whilst the newborn infants of affected mothers had generalised hyperpigmentation and hyperkeratosis.

Persistent hyperlipaemia affecting the triglyceride fraction of the serum was however the most consistent finding. It had only been reported twice before from trichlorophenol by Dugois[20] and by Goto who reported even more severe elevation of serum triglycerides in 10 cases of pentachlorophenol poisoning[42].

CLINICAL FEATURES

In almost every report, whatever the causative chemical, the clinical features have been most consistent[77].



FIG. 8.—Typical case of pitch acne.

The most distinctive and almost invariable cutaneous lesion, usually absent in oil acne and rarely seen in pitch or tar-acne (Fig. 8) both of which are also more inflammatory, is the chloracne cyst[66]; skin coloured, varying from 1 mm even to 1 cm in diameter, and with the central opening difficult or impossible to detect (Fig. 7.).

If these cysts are absent then chloracne should be diagnosed with great caution, except in early or very mild cases. Comedones and small cysts are therefore the basic lesions and may be very few or so numerous as to present confluent sheets. Inflammatory papules and pustules are not so common, much less so than in oil acne, and are almost invariably associated with friction from clothing, being commonest therefore on the back of the neck, shoulders, chest, genitalia, buttocks and thighs, and affecting only the more severe cases. Acne from paraffinic oils and tar products are both more inflammatory than chloracne, especially the first named.

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FIG. 7.—Typical case of chloracne.

DISTRIBUTION

This is predominantly facial even when the poison has been ingested, the malar areas, jaws and behind the ears being sites of particular predilection. In mild cases these areas alone may be involved. The nose is invariably spared except when poisoning is systemic. This distribution is not specific to chlorinated aromatic hydrocarbons but to any acneigenic fume or dust for, as we shall see, acne from pitch fumes behaves in exactly the same way. With increasing severity the rest of the face and neck soon follow, whilst the outer upper arms, chest, back, abdomen, outer thighs and genitalia may be involved in varying degrees in the worst cases. The flexures, hands, legs and feet escape in almost every case.

ADOLESCENT ACNE

The predisposing effects of adolescent acne, so often quoted, have no sound statistical backing so that the question must remain unanswered.

PRURITUS

This is more difficult to assess, reports of its occurrence being fairly evenly divided[27,44,77]. Although no-one volunteered it, in response to a direct question a little under half of my own cases admitted itching, Of a series of clinic patients with acne vulgaris the same question met with an almost uniformly negative reply. It is therefore possible that where itching is not mentioned in the literature it was neither asked about nor volunteered. In no single report of chloracne from any substance other than chlornaphthalenes, including the numerous and meticulously investigated Japanese cases of systemic tetrachlordiphenyl poisoning, has itching once been mentioned. Pruritus may therefore be specific to chlornaphthalenes but without more evidence this must remain speculative.

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DURATION OF EXPOSURE BEFORE ONSET

This is usually irrelevant because the degree of exposure is so variable. One can only say that even with external contact of the grossest kind most authors agree that four weeks or more are needed for lesions to appear.

PROGNOSIS

The prognosis both as regards the duration of the lesions and degree of scarring is naturally dependent upon the severity of the disease. This will be seen in greater detail when considering my own cases. Some of the worst recorded instances of scarring have followed exposure to various chlorophenols, possibly due to the intense toxicity of the chlordibenzodioxanes probably involved.

HISTOLOGY

Findings in the experimental human subject have been confirmed by those in the rabbit ear canal[34], in both cases hexachlornaphthalene being the acneigenic agent used.

First of all there is a steady thickening and hyperkeratosis of the epithelium in in the infundibulum of the pilosebaceous follicle. This is accompanied by a slow disappearance of the sebaceous glands, until eventually a keratin filled syst-like dilatation is formed. In some cases the exit is tiny whilst others are little more than a shallow trough. Shelley[69] suggested that the disappearance of the sebaceous gland was due to back pressure but accepted that squamous metaplasia occurred as previously shown by Eisen et al. in 1955[25]. Hambrick[35] with serial biopsies showed that the disappearance of the sebaceous glands had already begun five days after the first acneigenic applications, long before any back pressure was possible, and thereafter steadily progressed. He therefore suggested that chloracne producing chemicals initiated squamous metaplasia and that when all sebaceous material present had been shed a large, dilated, squamous epithelium lined and keratin filled pilosebaceous follicle was formed. There is of course general agreement that, as in acne vulgaris, rupture of the follicle produces the inflammatory process.

TREATMENT

Most authors have accepted it as hopeless but strong exfoliants in the hands of Dussart[22] cleared 56 mild cases in from one week to five months. Dermabrasion was successfully used by Hubler[40] and also by myself. Dugois[21] claimed success from the intravenous infusion of calcium ethylenediamine tetracetic acid in very severe cases of chloracne and poisoning from trichlorophenol residues but no details of his results were given. Otherwise expression of comedones and incision of cysts has been the stand-by of most physicians, but with little success.

CHLORACNE IN A PAPER CAPACITOR PLANT USING TRI/TETRA AND PENTA/HEXA CHLORNAPHTHALENES FROM 1956 TO 1963

Very briefly a capacitor or condenser is a means of storing and suddenly discharging electrical energy. Basically it consists of an insulator or dielectric between two conductors each with a terminal. The majority consist of a sheet of paper sandwiched between two sheets of thin metal foil a long length of which is rolled up like lavatory paper to provide a large surface area. In this particular process the rolls of foil and paper with their terminal wires were packed into, and pressed flat in metal clamps used over and over again by four women seated very close to the drying ovens and impregnating vessels. After drying for 24 hours at 115°C to remove every trace of

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moisture from the paper, racks of capacitors were heated in a vacuum vessel for 24 hours at 110°C and then impregnated with molten tri/tetrachlornaphthalene run in from a reservoir.

After pumping out the molten wax the impregnated units were removed by hand, cooled and passed to the dipping section. If supply exceeded demand impregnated capacitors were stored by embedding them in the impregnating wax in metal trays to prevent ingress of moisture. When ready for dipping this wax was melted in the ovens and the racks of units removed. Exposure to tri/tetrachlornaphthalene fumes was very gross indeed in this section for the following reasons :—

1. Fuming of molten wax residues at 110°C when emptying impregnating vessels.
2. Failure to realise that fumes from wax remaining on clamps from previous impregnation would escape constantly from the non-airtight and unventilated ovens.
3. Melting out in the ovens, trays of stored capacitors.

Nevertheless, during its existence from 1956 to 1963 no single case of chloracne occurred among workers in this section, thus indicating most clearly the non-acneigenic nature of tri and tetrachlornaphthalene fumes. After impregnation the unit was dipped into a tougher wax melting at 130°C and consisting of roughly equal parts of penta- and hexachlornaphthalene with 5% pentachlordiphenyl as a plasticizer. This dipping section was a long narrow area inside the main workshop enclosed by partitions 7 ft. high. There were two dips, the first in vacuo at high temperature and the second a cooler one at atmospheric pressure. After dipping the wax was removed from the terminal wires by dipping them in molten solder on which floated a metal plate with a hole in it. This both cleaned and retinned the wires in one operation at the same time unfortunately vapourising the chlornaphthalene. Then the performance data were painted on the capacitor and finally it was coated with an isocyanate resin. The fume escape from dipping was severe. This was due to :—

1. Ineffective extraction which in any case only partially covered the fume production from the dipping vessels and their electrically heated replenishment tanks.
2. Removal of units from the dipper whilst still wet and fuming strongly.
3. Cleaning out the dipping tanks weekly. This led to gross fume exposure for two to three hours every week. The molten wax at 160°C was ladled out by hand into trays, the residue removed by a drain cock under the vessels and trichlorethylene added, the lid screwed down, the mixture boiled and then drawn off. The stop cock was closed and fresh solid wax added.

Other sources of penta/hexachlornaphthalene fumes were the evaporation by molten solder of all the wax on the terminal wires, the extraction being too weak ; and the drawing of a current of fume laden air from the dipper and the wire tinners to the very powerfully extracted lacquering bench, thus secondarily exposing three further workers to a fume hazard. The first was the printer and the others the lacquerers especially the two nearest the dipper. The fact that some of the lacquerers developed chloracne only on the fume exposed side of their faces proves the external nature of the chloracne stimulus in this process.

In 1958 extraction was increased but was still inadequate and no further change was made until October 1960 when dipping was totally enclosed, wire tinning very powerfully extracted, and the layout of the process opened by the removal of all partitions. To the Company's despair chloracne continued to occur, though much less severely, among the dippers and wire solderers. Careful observation of the process soon revealed that tiny wisps of fume escaped occasionally even from the enclosed dipper, due to exhaust vents becoming choked with sublimed chlornaphthalene.

Furthermore wire solderers on piece work could, if working very fast, remove an occasional unit from the exhaust hood whilst a tiny wisp of fume remained to contaminate the air. This well illustrates the chloracne producing potency of even the

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smallest regular fume exposure to penta and hexachlornaphthalenes, an important observation not true of the equivalent chlorinated diphenyls.

Alternative materials had been urged for a long time and finally a mixture of three parts of tri/tetrachlornaphthalene and one part of polystyrene provided a satisfactory alternative. From the time of its adoption chloracne ceased, again confirming the non acne-producing nature of chlornaphthalene with less than five chlorine atoms per molecule.

Because of the constant variations from hour to hour and day to day, any attempt to relate fume level in milligrams per litre to the degree of chloracne would have been too inaccurate to have had any practical value and was not attempted. For the same reason it is valueless to record the time taken for chloracne to appear except to say that the grosser the exposure the more rapidly it developed and vice versa.

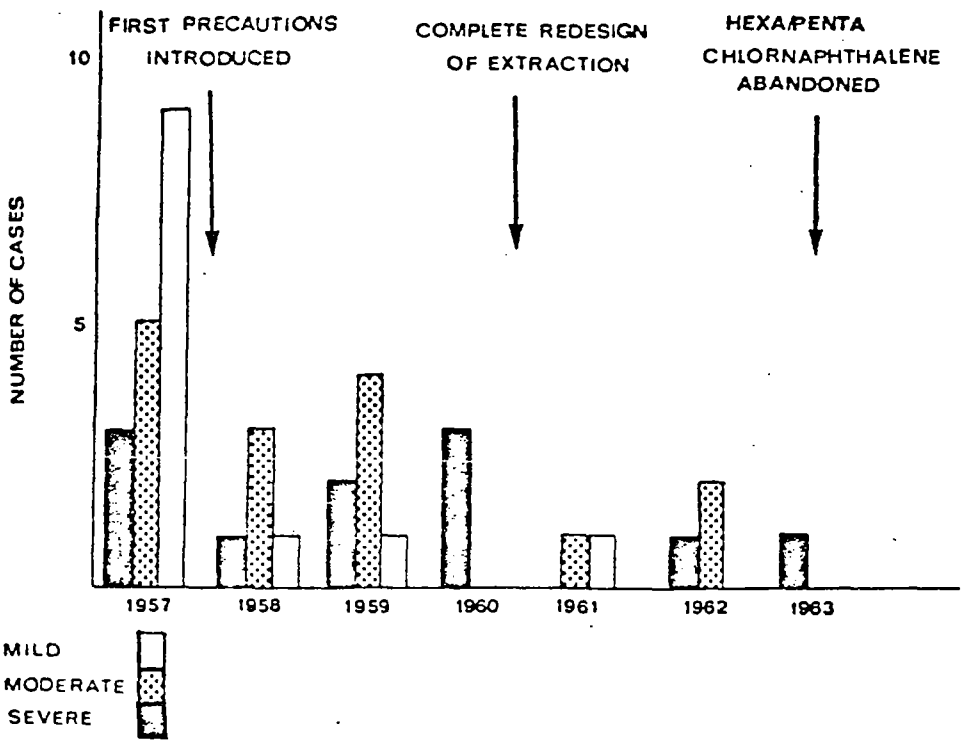

FIG. 4.—Incidence of chloracne in capacitor plant.

Similarly, and also because of continuous turnover, any figures relating the number of cases to the total at risk would be highly inaccurate and will not be presented. When the labour force had been static for a long time, however, at my first inspection in 1957 almost every worker in the dipping section had chloracne.

Fig. 4 clearly shows the progressive improvement following the institution of preventive measures at the end of 1957 and again after almost total enclosure of the process late in 1960. The increased percentage of moderate and severe cases after the initial precautions was due to the elimination of general fume level which had previously caused many indirectly exposed mild cases, whilst quite severe fume exposure continued at special points.

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Fig. 5 emphasises the concentration of lesions on the malar areas and this appears to be an essential feature of fume exposure as we shall see in the comparison of acne due to pitch fumes. Although cysts are almost always present in chloracne, very mild cases may present a few comedones only. It can be seen that inflammatory lesions

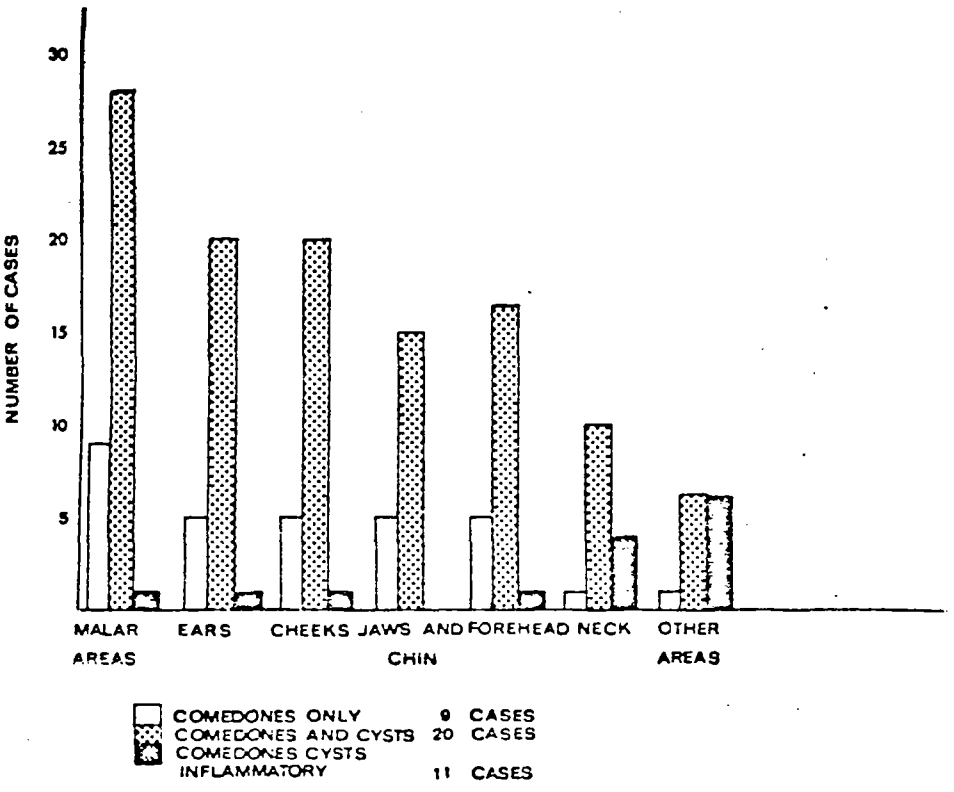

FIG. 5.—Distribution and type of lesions in 40 cases of chloracne.

were almost always associated with clothing friction but cysts and comedones were always present in these areas also, again a sharp distinction from pitch acne and I believe an important one.

Fig. 6 shows the duration of the disease. Whilst the vast majority of cases clear within four years, some of the severest ones still have lesions even at ten years. One unexpected finding was the fact that no less than 45% of patients, up to ten years after they regarded themselves as clear, still had small numbers of residual black heads and occasional small cysts which, despite constant squeezing, had consistently re-appeared. There was scarring of severity in 10%, all of them being severe cases with inflammation. In 25% there was a very fine pitting of honeycomb atrophy type on the cheeks and in the remainder none at all. It must be remembered that all the above data refer only to penta and hexachlornaphthalene and cannot therefore necessarily be assumed to be true for other chloracne producing materials.

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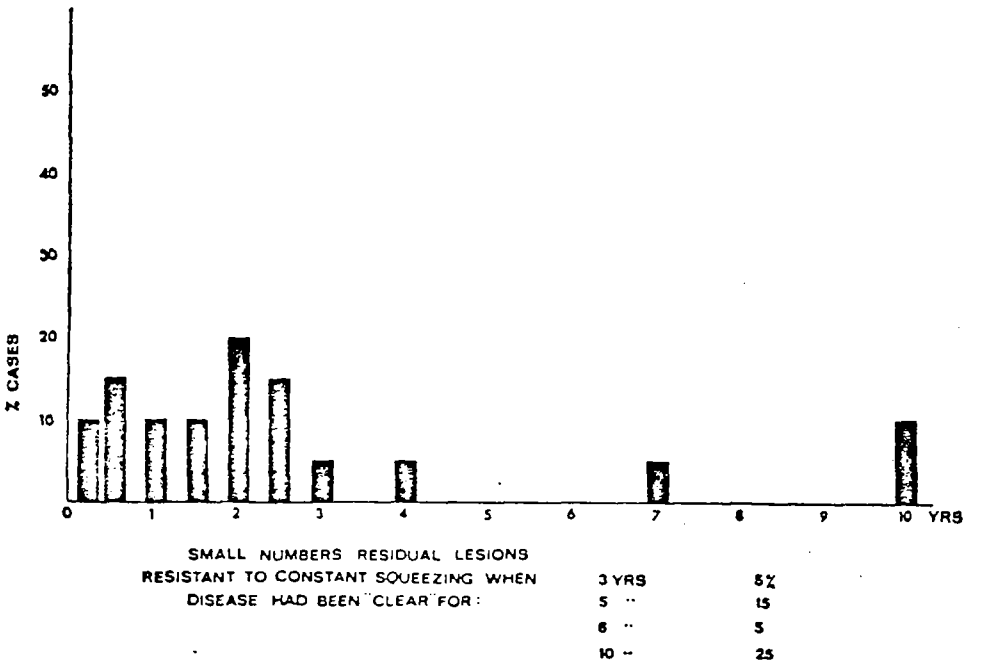

FIG. 6.—Duration of chloracne.

PREVENTIVE MEASURES

The main preventive measures adopted were based on those proposed by Cranch(15) :—

1. Complete extraction of fumes (which was never achieved).
2. Neck and wrist fitting white overalls changed daily and cleaned in trichlorethylene.
3. Frequent and thorough washing.
4. No eating or drinking in the plant.
5. Rapid turnover of workers until extraction was perfected in order to minimise the duration of exposure.

PITCH ACNE

I now intend very briefly to compare chloracne with the clinical details and prognosis of a series of 54 cases of acne due to fumes from pitch. Since the exposure was virtually identical in each series of cases any clinical and/or prognostic differences should be significant.

The exposure in this case arose in a plant moulding various objects from a thermoplastic material consisting of a mixture of molten pitch, asbestos, and powdered slate. From a mechanical mixer it was removed in large masses like baker's dough on to metal trolleys. They were then removed to thermostatically controlled ovens set ostensibly at 180°C but often much higher due to malfunctioning thermostats. These were not extracted at all and when opened fume exposure was great.

From the oven the specified amount of hot dough was taken out and weighed on a work bench on kitchen type scales and then beaten with an iron bar. It fumed most

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strongly during all these operations and the extraction, which was of poor quality, was high up and only over the work bench. Its effects therefore was to draw the fumes from the beaten dough up into the worker's face. Fume exposure was gross and continuous. The cooling mass was then removed to a hydraulic press for moulding.

Despite the wearing of asbestos gloves, wiping dirty hands on the legs of trousers accounted for the high incidence of folliculitis on the thighs.

Fig. 9 shows even more clearly than in chloracne the great predilection of the malar areas in response to fumes. The purely comedonic nature of the facial lesions is most striking and in marked contrast to the mixture of comedones and cysts present in most cases of chloracne[9]. The description of similarly profuse comedonic eruptions in some of the older accounts of so-called chloracne from trichlornaphthalene again points to pitch as the probable hazard in these cases, mentioned earlier in this paper[14,49].

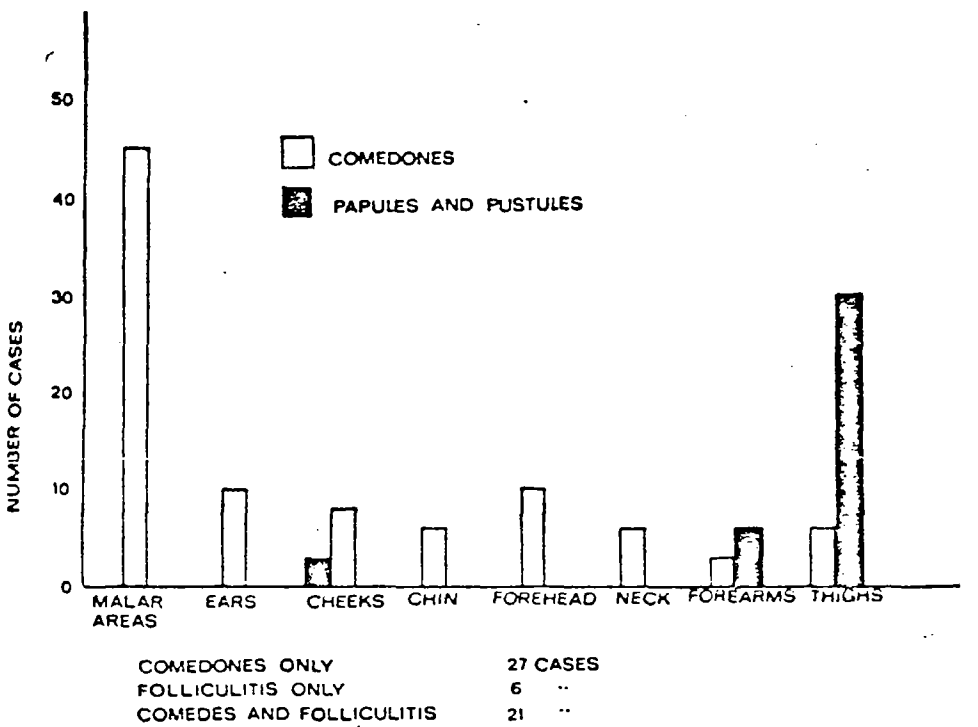

FIG. 9.—Pitch acne. Distribution and type of lesions in 54 cases.

The inflammatory lesions although again, as in chloracne confined to areas of clothing friction were, in great contrast, almost uniformly devoid of blackheads. Again, unlike chloracne, folliculitis was seen in six cases without any comedones at all even on the face.

There were several cases in whom small numbers of residual blackheads remained for many years. These patients, like the chloracne ones, were insistent that these comedones were not present until the industrial acne developed.

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The main differences from chloracne were therefore as follows :—

1. The cysts so typical of chloracne were rarely observed.
2. There was an eruption of pure comedones on areas exposed to fumes without friction.
3. Papules and pustules i.e. folliculitis, on the thighs and forearms were rarely accompanied by comedones but were relatively common.
4. In general pitch acne clears much more rapidly than chloracne and scars less but, as with the latter, many men had a few persistant comedones which, despite regular squeezing, were still reappearing even ten years later.

CONCLUSION

And now I hope you will forgive me if I conclude with the obvious. Despite the problems posed by difficult management and industrial relations as I know only too well, in the investigation and reporting of every outbreak of industrial disease the attempt must be made to observe certain minimal criteria.

The first and by far the most important is accurate information on the chemistry concerned, which includes not only information from the users' engineers and chemists but, much more important, the chemical manufacturer of the basic materials. In this connection the role of contaminants or unwanted reaction products must never be forgotten, may indeed be critical, and must always be investigated[16,45].

Now to suggest that no report of industrial disease is complete without a full description of the process concerned and the exact point or points at which those affected fit into them seems almost absurd, but it is astonishing how often in the literature these simple facts have been omitted[31,72].

Finally, much experimental work remains to be done. Although the usual warning is necessary when interpolating between the experimental and the human animal, a good correlation appears to exist between acneiform lesions produced by external contact on the rabbit ear and chloracne in man. Furthermore, as far as it goes, in the only two recorded outbreaks of chloracne in man from ingestion of chlorinated aromatic hydrocarbons both compounds have also been capable of producing chloracne on the skin of man and the rabbit ear by external contact[32,42].

This correlation is important because of the much greater difficulty of producing in experimental animals chloracne-like lesions from ingestion of the suspected toxic substance and the impossibility of doing so in human volunteers. A great extension of work on the rabbit ear as well as further investigation into the fascinating hyperlipaemia with a variety of commercial and highly purified aromatic chlorinated hydrocarbons would therefore seem to be potentially rewarding.

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