OCCUPATIONAL RESPIRATORY DISEASES

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Smelters
Welders

- **Polymer fume fever:**
  Fabrication of fluorocarbon polymer products by:
  extrusion
  moulding
  sintering
  Solderers, cutters and welders of metal parts coated with or in proximity to fluorocarbon polymers or telomers as in the automotive and electronics industries and in the manufacturing of domestic and laboratory equipment.
- Organic dust fever which may be due to bacterial endotoxin and, questionably, mycotoxins.
  probable:
  cottonseed oil operators
  cotton ginners
  cotton textile workers
  grain handlers
  grain inspectors
  weavers
  cotton classers and warehousemen
  cotton waste utilization workers
  possible:
  Many theoretically at risk but no data is available. Farm workers, particularly those involved in confinement animal husbandry. Workers in artificially humidified environments as in the manufacturing of synthetic fibers.

EPIDEMIOLOGY

There has been little interest in conducting epidemiologic studies on this group of occupational fevers. This is probably because of their limited duration, relatively nonserious nature, and because tolerance to repeated exposure often occurs. The limited epidemiologic resources available have rightly been devoted to more serious occupational diseases and particularly to chronic nonreversible effects. A classic function of epidemiologic studies is to relate prevalence of disease to exposure and from this to determine dose-response relationships. This is particularly difficult in the group of occupational fevers for two main reasons. First, as tolerance to exposure often develops and no objective residua are detectable, investigators must rely on questionnaire information—seeking a history of work related febrile illness, often years in the past. This is unreliable and easily confused by the worker with an infectious illness. Prospective studies of new workers which might alleviate this problem have not been reported. The second problem, relating to the dose, causes great difficulty because of the complexity of the occupational environments in which this group of conditions occur. Metal fumes invariably contain the oxides of several metals; polymer fumes are highly complex and vary considerably with the temperature at which they are generated; both endotoxins and mycotoxins occur together with a vast array of other complex substances in organic dusts. The limited data which are available provides no dose-response information and should be considered relatively unreliable as far as the disease prevalence is concerned.

Many reports of metal fume fever state that the condition is "common" among new workers but do not give further information. Brodie, in a study of an unspecified number of welders in shipyards, stated that 20% had chills and fever occasionally while 5% had frequent episodes (19). Bachelor et al., investigating disease in workers handling finely divided zinc oxide and sulfide, produced a similar proportion (6). They found that 9 of 24 workers reported reactions and of these, three had occasional and one frequent recurrences. In a more thorough study by Ross, 530 welders aged 20 to 59 were interviewed and 116 (22%) reported a history of metal fume fever (94). Many of these workers related their symptoms to welding galvanized metal, particularly in an enclosed environment. Exposure to finely divided copper dust generated while polishing copper plates was investigated by Gleason (48). He implied that all exposed individuals suffered symptoms and that these were prevented by reducing the concentration of copper from between 78 to 120 $\mu g/m^3$ to 0.8 $\mu g/m^3$. Fumes generated from ferro-chrome alloys produced symptoms in 20 of 40 tappers who were highly exposed while only one of 30 less exposed workers in the same plant reported problems (106). These studies only give a rough indication of prevalence and provide no information on the response to different exposure situations.

There is also minimal epidemiologic data on the prevalence of effects due to pyrolysis products of fluorocarbon polymers. In a study of 77 workers in a small PTFE fabricating plant, Polakoff et al. found that 60 (86%) had experienced febrile reaction at some time and that

14 (18%) reported multiple episodes in the previous year (91). The observation that most of the reported episodes were more than a year in the past suggests the possibility of the development of tolerance. Concentrations of PTFE particulates were in the range 0-2.4 $\mu g/m^3$, but decomposition products were not measured.

A prevalence of 47% (14 of 30) was observed by Adams in workers processing PTFE (1). Some environmental sampling was carried out, but no conclusions can be drawn as to dose-response. Multiple episodes of fever were reported; the majority of the reactors were smokers. This relationship between smoking cigarettes and polymer fume fever has been stressed in many reports. Wegman and Peters found 7 of 13 workers exposed to a heated liquid fluorocarbon telomer, used in the production of synthetic crushed velvet, gave histories of polymer fume fever (118). All affected workers were cigarette smokers. Many authors considered the smoking of cigarettes accidentally contaminated by fluorocarbon polymers to be an important route of administration. Dose-response studies using contaminated cigarettes were reported by Clayton (26). He observed that smoking one cigarette contaminated with a minimum of 0.4 mg of tetrafluoroethylene telomer would produce a pyrexial illness and that approximately the same amount was required on a cumulative basis in which cigarettes each contained 0.05 mg. It is likely that ill effects due to smoking contaminated tobacco are responsible for a large proportion of polymer fume fever cases. This is clearly important in its prevention.

Reported prevalences of pyrexial illnesses induced by organic dusts differ greatly. This is not surprising due to the marked variability of such dusts and the subjective way in which data are collected. There is no dose-response information even at the level of total or respirable dust, nor have symptoms been related to the concentration of endotoxin in the dust. Indeed, though it is likely that endotoxin is important in generating fever in individuals exposed to organic dust, this is not proven. It has recently become possible to measure endotoxin using the sensitive Limulus amebocyte lysate test (30). Although this test may give positive responses with other substances (37), these are not likely to be present in the occupationally important dusts. Olenchock and Major reported levels in grain dusts of the order of 0.4 $\mu g/gm$ (87). Kutz et al. obtained a similar concentration in cotton dust (65). These values are probably more reliable than previous estimates of 3 to 11 mm/gm in cotton dust measured by Pernis et al. using other less sensitive methods (89). Even assuming high concentrations of whole dust in the working environment, the dose of endotoxin taken in during an eight-hour shift might be of the order of 0.1 μg. If this estimate is correct, it is debatable whether such a small amount would induce pyrexia when inhaled. This raises the possibility that other agents present in the dust might be important.

In early reports of mill fever in the cotton textile industry, it is implied that febrile reactions are common among new employees; prevalences are not reported. Prevalences of pyrexial illnesses in new workers, ranging from 10% to 50%, were reported in 37 cottonseed oil mills studied by Ritter and Nussbaum (92). In the cotton textile industry Werner found that 26 of 414 cardroom operatives suffered febrile illness (120). Schilling obtained a similar prevalence of 7.2% in a study of 528 workers(96). The latter author noted that a prior occurence of mill fever had no relationship to the later development of byssinosis. Similar variation has been reported in grain handelrs' fever. These have varied from a high of 18 out of 55 (32.7%) reported by Kleinfield (64) to a low of 6 out of 441 (1.4%) reported by Broder et al. (20). Even in s situation in which extreme exposure to exdotoxin occurs, not all workers suffer illness. Of 30 workers exposed to an aerosol of dried sewage at total dust levels up to 4 mg/m^3 only one-third had febrile reactions (70). Though endotoxin concentration is not known, heat treated dried sewage must be very rich in endotoxin. This again indicates the need for further work on the relationship of endotoxin to occupational pyrexial illness. Other workers, particularly in farming, are exposed both to endotoxins and mycotoxins, No epidemiologic information is available.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The group of conditions discussed in this section are usually short-term pyrexial illnesses which are self-limiting and often only occur following initial (few) exposures in a proportion of new workers. Though the symptoms may be temporarily incapacitating—and with high exposure, may result in pulmonary edema—no ob-

jective evidence of the illness remains and no permanent impairment has been reported. Prevalence data based on questionnaires have varied greatly from study to study. No reliable prevalences are available which are representatives for the total exposed population.

Because tolerance develops rapidly with exposure to organic dusts (endotoxin) and to metal fumes, only new workers or those who have avoided exposure for some time are at risk of developing symptoms, The proportion of the total work population truly "at risk" is therefore indeterminate. It is debatable whether tolerance to fluorocarbon polymer pyrolysis poducts occurs. NIOSH estimates that 5,000 workers are potentially exposed and may all be at risk of developing symptoms.

PATHOLOGY

Short-term pyrexial reactions of an influenza-like nature consequent to occupational exposure have been recognized for many years. Thackrah gave a clear description of metal fume reactions in 1832; Arlidge described the pyrexial reaction to dust in the textile industry, "mill fever," in 1892. Despite this early recognition, there is very little systematic research on the pathology and pathogenesis of these pyrexial reactions following respiratory tract exposure. There are many studies of bacterial endotoxin reactions. Stemming initially from the development of injection therapy in the latter part of the 19th and early part of this century, research concentrated on injection effects rather than respiratory tract exposure. Mycotoxin research is more recent, but again respiratory tract exposure has been relatively ignored because the effect of mycotoxin ingestion in spoiled food was the overriding concern. The effects of fume inhalation from heated fluorocarbon polymers was first recognized in 1951 (53), but research into the mechanisms of the acute reaction is scanty.

Syndromes produced by diverse agents are similar. All involve a lag period of several hours between exposure and first effects; all involve a neutrophil leukocytosis and pyrexia; all are usually self-limiting, resolving within approximately 24 hours. Symptomatology of "aches and pains," chills shivering, general malaise, headache, cough, and other respiratory tract symptoms (and sometimes nausea and vomiting) are common to all. Especially interesting is the development of a tolerant state on repeated exposure. This is clearly documented with repeated exposure. This is clearly documented with repeat exposure to endotoxin and metal fumes and has been demonstrated in rabbits to the particulate component of polytetrafluoroethylene fumes (24). There are not studies on possible tolerance to mycotoxin exposure.

Metal Fume Fever

In a series of five papers in 1927 and 1928, Drinker and his colleagues from the Harvard School of Public Health presented the first thorough experimental studies of metal fume fever in humans and animals. They reproduced the syndrome with very pure zinc fume inhalation in normal volunteers. They observed a polymorphonuclear leukocytosis commencing between 2-½ and 5-½ hours after inhalation, reaching a peak at about 9-½ hours, and lasting for about 36 hours. They demonstrated temporary decreases in vital capacity but no changes in chest radiography (107). They demonstrated tolerance to zinc fume exposure on consecutive days and noted that a leukocytosis did not occur on the second exposure (34). The same group also showed that finely divided zinc oxide powder (0.4 μ in size) and magnesium fumes produced the same effects (35). Drinker & Drinker studied the effect of zinc and magnesium fumes on cats, rats, and rabbits (32), and confirmed an earlier observation: rather than a pyrexia, a fall in temperature resulted (112). They also demonstrated an outpouring of polymorphonuclear leukocytes into the airways. Vigliani and his group were able to induce fever in rabbits by exposing them first to an aerosol of dilute acetic acid, followed by zinc oxide fume (89). Control rabbits exposed to acetic acid alone did not develop fever. They demonstrated tolerance on repeated exposure and showed that this did not cross-tolerate to bacterial endotoxin. They were able to demonstrate endogenous pyrogen in the serum of exposed rabbits and postulated that the mechanism of metal fume fever involved the direct liberation of leukocyte endogenous pyrogen by metallic oxide [see review by Atkins, 1960 (4)]. They noted that on histologic examination, the pulmonary capillaries of zinc-exposed rabbits were filled with polymorphs. Hence a close contact between zinc fume and leukocytes was possible. Ohmoto et al. also demonstrated the pyrogenicity of zinc and a variety of welding fumes in the rabbit (85). In this series of experiments the fume was given intravenously as a suspension. They were able to show the development of tolerance to zinc fume after two

doses, at weekly intervals, but failed to show tolerance to welding fume which contained metals other than zinc. They were unable to induce fever with commercial zinc oxide, metallic zinc, the coating materials of the welding electrodes, commercially available iron oxides (ferrous and ferric), and oxides of manganese, silicon, aluminum, magnesium, and cadmium. This work, therefore, provides evidence that metallic oxides must be nascent (i.e., freshly generated) to induce fever.

The same group of workers demonstrated that the pyrogenic component of welding fume was present in the particulate portion of a watery suspension (86). It was thermostable in suspension. It became inactive when desiccated by heat but not when desiccated by lyophilization. This suggests that either particle size or crystal structure might be important in the induction of fever.

In following up this work, Mori et al. showed the pyrogenicity of zinc, lead, and magnesium fumes on inhalation by rabbits depended on the presence of carbon monoxide in the fume (77). Only small amounts (less than 0.01%) of CO were necessary. Leukocytosis occurred both with and without the presence of carbon monoxide in the fume. The authors suggest the reaction of carbon monoxide with the metallic oxide results in the formation of a catalytically active N-type semiconductor. This (they suggest) is the component of welding fume which induces the fever. McCord speculated on the possible immunologic causation of metal fume fever and tolerance induction (71). He suggested an immune response to a metal proteinate as the causal mechanism with an antibody as the mechanism of tolerance. There is no evidence to support this hypothesis and it is immunologically unconvincing.

Summary

The pathogenesis of metal fume fever involves the induction of a peripheral blood and airways leukocytosis by an activated or nascent metallic oxide. The mechanism for this is not known. There is evidence to suggest that fever results from the liberation of endogenous pyrogen, probably from leukocytes. The mechanism of tolerance is not known, but cross tolerance to endotoxin does not occur in rabbit experiments.

Polymer Fume Fever

The products produced on heating this group of substances depend primarily on the temperature and environment in which the reaction takes place. At lower temperatures the monomer from which the material is produced is the principal product. At higher temperatures a range of perfluro compounds containing 3-5 carbon atoms and a particulate fume with a particle size of 0.2-0.5 μm is found. At still higher temperatures carbonyl fluoride is produced. This compound readily hydrolyzes to hydrogen fluoride and carbon dioxide in the presence of water vapor. Many other pyrolysis products have been identified in smaller amounts. A review of the pyrolysis process and products produced is presented in the 1977 NIOSH criteria document for a recommended standard for occupational exposure (80).

Harris first described the clinical picture of polymer fume fever (53). He noted its similarity to metal fume fever but did not document a detailed investigation. He noted that in cases reported to him by a colleague, a leukocytosis had been present. Because of the similarity to metal fume fever, Harris analyzed PTFE ash and sublimate for metals. He concluded that metals could not be responsible. Bruton was the first to suggest the smoking of cigarettes accidentally contaminated with fluorocarbons was an important means of exposure (22).

A detailed investigation of an inflight illness in 35 individuals by Nuttal provided more information (83). He traced the illness to PTFE incorporated in asbestos tape wrapped around an exhaust manifold. This vaporized because of the heat of the manifold. He confirmed the occurrence of a polymorph leukocytosis with an increase in young forms both in the aircraft passengers and in one volunteer experimentally exposed to heated tape.

Chest radiographic changes, which resolved within 72 hours, were described by Robbins and Ware (93). These were found within a few hours of exposure to heated PTFE. Changes consisted of bilateral diffuse infiltration which the author interpreted as pulmonary edema. Evans reported further evidence of pulmonary edema on chest x-ray in a worker who used an oxyacetylene torch to dismantle a metal table contaminated

with a tetrafluoroethylene telomer (40). The x-ray changes resolved completely over a seven day period.

Exposure to one of the perfluoro breakdown products (perfluoroisobutylene) in laboratory workers was reported by Makulova (67). The duration of exposure was brief (less than one minute), but the concentration was not known. As perfluoroisobutylene is only one of many trace products produced by heating flourocarbons (116), it is likely that exposure to the pure compound was more intense than usually received in the workplace.

All five patients exposed to perfluoroisobutylene showed x-ray changes developing within 4-6 hours. In four patients, the changes were consistent with pulmonary edema, but the fifth had multiple small opacities. One patient died; the autopsy findings were of pneumonia and pulmonary edema with a hemorrhage in the left adrenal. This patient had suffered from pneumonia two months before exposure and this could conceivably have made her more vulnerable. These several reports of pulmonary edema are cause for concern, suggesting that polymer fume fever is not always the benign, short-term pyrexial illness most consider it to be.

There have been a number of experimental studies on whole polymer fume effects on animals and of selected components thereof. These have demonstrated that at high concentrations, pulmonary edema, pulmonary hemorrhages, and death are produced (23)(24)(97)(116). Production of leukocytosis in animals has proved to be difficult as in the case with metal fumes. Cavagna et al. reported both pyrexia and leukocytosis, preceded by a decrease in body temperature, with the same technique they had used in their metal fume fever studies (24). They preceded the inhalation of PTFE fume by an inhalation of dilute acetic acid. They were also able to induce fever by the intravenous injection of washed fume particulate and by this route induced a tolerant state. As in the case of metal fume fever, there was no induced crossed tolerance to *E. Coli* endotoxin. Blagodarnaya confirmed pyrogenicity of the particulate phase of PTFE fume (14), however, washing the particles or storing them for six months abrogated this response. Further evidence supporting the importance of the fumes' particulate phase is provided by Waritz and Kwon (116). They found removal of the particulate by filtration abolished mortality and pulmonary pathology in rats. Filtration did not significantly reduce hydrolyzable fluoride levels; they were in the range where the presence of particulates causes pathology and death. Thus filtration reduced mortality form 6/6 to 0/6. They suggested the particulate carried toxic products into the alveoli, because the particle size range was 0.5-2μm. In view of the conflicting results using washed particulate, this question is still undecided.

Summary

Polymer fume fever is similar to metal fume fever; it involves peripheral blood and airways leukocytosis following the inhalation of the particulate phase of fluorocarbon polymer fume. Radiographic evidence of pulmonary edema has been reported in some human cases and has been produced on intense exposure in animal studies. Unlike metal fume fever, tolerance to repeated exposure is not clearly documented in man, however, it has been demonstrated in rabbits with repeated intravenous injection of a fume particulate suspension. The participation of endogenous pyrogen in the febrile response has not been demonstrated but was postulated by Cavagna et al. based on the synchrony of leukocytosis and fever and on the degranulation of polymorphs after phagocytosis of particles *in vitro* (24).

Organic Dust Fever—An Endotoxin Effect?

Medical science has been interested in the effects of endotoxin, for a variety of reasons, since the latter part of the 19th century. Initial research was stimulated by the observation that injection of a variety of substances, particularly by the intravenous route, would induce fever and various symptoms of an influenza-like nature. Injected materials included distilled water, saline, therapeutic agents such as salvarsan, colloidal metals, and bacterial vaccines. Reactions were eventually traced to the presence (in the solutions) of heat stable pyrogens of bacterial origin (58)(98). Research continued (a) because of the possible therapeutic value of induced fever in such conditions as neurosyphilis, gonorrhea, and other diseases (54), and (b) because of the growing use of bacterial vaccines in the prophylaxis of disease. Further research into bacterial pyrogens derived from the use of Coley's fluid in the treatment of cancer (81). Basic research into the mechanism of fever provides an abundant literature on the effects of bacterial pyrogens as they

are a ready means to induce febrile reactions in experimental animals. Recent research has been devoted to the role of endotoxin in human shock, particularly in relation to abdominal surgery in poor risk patients.

Bacterial endotoxin has been suggested as a cause of a variety of occupational disease conditions. These include mill fever, weaver's cough, mattress makers' fever, bible printers' fever, humidifier fever, byssinosis, grain fever, bagassosis, farmer's lung, and others (90). Some of these occupational illnesses have been subsequently shown to be due to other agents—notably bagassosis and farmer's lung (see section on Hypersensitivity Pneumonitis)—while the case for the role of endotoxin in the etiology of byssinosis is poor (see section on Byssinosis). Two major problems exist when attempting to relate occupational health data with the large body of literature on endotoxin. 1) In the occupational setting, endotoxin enters the body by the respiratory tract, whereas virtually all endotoxin research has involved the injection route, usually intravenously. 2) Of even greater difficulty, is that in the workplace endotoxin is invariably present in dust associated with an array of many other complex substances. This makes determination of the specific effects of endotoxin difficult or impossible.

Endotoxins are characteristically present in gram-negative bacteria. They form an integral part of the organism and unlike exotoxin are not secreted by living bacteria. They are released from the organism on death and autolysis. Originally studied by Boivin and Mesrobeaunu (15) and consequently often referred to in early literature as Boivin antigens, they have a molecular weight of between 10^6 and 10^7 daltons (110). Endotoxin is stable on storage and heating, requiring about two hours at 160 °C for inactivation. It is more labile in alkaline solution (9). Endotoxins are made up of a complex of phospholipid, polysaccharide, and protein. The phospholipid, lipid A, is responsible for the toxic and pyrogenic effects of endotoxin; the polysaccharide carries the principal immunogenic determinants specific for the organism from which it was derived. The determinants are made up of small numbers of hexose or pentose units and endotoxin from a single species may have several such determinants. Because of this, cross reactivity between species is common. The sugar determinants constitute the somatic or "O" antigens of the microorganism. Lipid A in isolation has low toxicity because of its insolubility. It regains toxic activity when conjugated to a carrier molecule as in its natural state (11). The detailed structure of endotoxin is reviewed by Morrison and Ulevitch (79).

When given intravenously to humans or experimental animals, endotoxin produces a characteristic sequence of events (4)(11). Fever develops within 15 to 50 minutes and may be biphasic in character—giving peaks at approximately 1½ and 3 to 5 hours. The character of the temperature curve depends on the dosage given. Pyrogenic reactions are readily produced in man, horses, dogs, cats, and rabbits, while guinea pigs, rats, and mice may fail to respond or may develop mild hypothermia. Associated with the fever are changes in the formed elements of the blood. If a sufficient dosage is given, an initial leukopenia precedes the pyrexia. This is followed by a leukocytosis involving mainly an increase in the number of immature granulocytes. A transient thrombocytopenia has also been reported. In man, the fever is associated with headache, myalgia, chills, and general malaise. Larger doses given to experimental animals result in peripheral vasodilation, visceral hemorrhages, shock, and death. These effects are produced by intravenous administration; the intramuscular and subcutaneous routes lead to slower and decreased responses, and in some reports, to absence of effect.

Only a limited amount of information is available on the effects of inhaled endotoxin. Pernis produced fever and dyspnea in less than 10% of rabbits exposed to an aerosol generated from a solution of 15 μg/ml (90). This occurred with latency of 30 to 50 minutes. If the rabbits were given repeated doses with intervals of at least two days, a high portion responded with fever and dyspnea. The same group of workers (25) were unable to generate either fever or leukocytosis in rabbits given an aerosol generated from 10 μg/ml of endotoxin. Using an extremely large dose, Snell did produce reproducible pyrexia in rabbits, however this was associated with leukopenia (103). Snell used an aerosol generated from 0.5 mg/ml. It is difficult to equate the inhalation dosage received by the rabbits with doses which would produce significant responses intravenously. Rabbits will produce pyrexia when given doses in the range of 0.0001 to 0.0003 μg/kg (4).

The rabbits in all these experiments received at least these small amounts by inhalation.

A number of studies have exposed human volunteers to endotoxin by inhalation. Neil et al., investigating an outbreak of an acute illness among rural mattress makers, isolated a gram-negative bacterium from stained cotton (82). They subjected three volunteers to a culture filtrate of this organism for a ten minute period. They responded by cough, chest tightness, headache, generalized aches and pains, and irritation of mucous membranes. There was a latency of about 45 minutes to 1½ hours and a leukocytosis with a predominance of young forms. Symptomatology lasted for approximately 24 hours. Studies of pulmonary function were not carried out. Although there undoubtedly would be endotoxin in the seven-day culture filtrate, it is impossible to know at what level this would be present. Pernis et al. also exposed man to endotoxin (90). They used concentrations of 20 μg/ml and obtained slight fever, a dry cough, and shortness of breath. The same group of workers exposed normal individuals to 40 to 80 μg of endotoxin total (25). They obtained neither pyrexia nor leukocytosis. However, two of eight of the normal individuals had a significant fall in FEV_1 and one of three individuals with chronic bronchitis also had increased airways resistance. On a weight-for-weight basis, man is more sensitive in his response to endotoxin than is the rabbit. Thus, 0.0005 to 0.002 μg/kg will promote a rise in temperature (4). This means the average man will respond to appreciably less than 1 μg on intravenous injection. It would seem likely that in all these human studies, more than this dose would enter the respiratory tract. As the work of Trejo and LiLuzio (111) and that of Mori et al. (76) suggests that lung tissue does not have great potential for the detoxification of endotoxin, it must be assumed that either endotoxin is bound locally without producing systemic effects, or that it enters the body rather poorly from the respiratory tract.

There is sparse literature on the histopathology of endotoxin inhalation effects and no studies on the pathogenesis of the changes observed. Using repeated doses, over a five month period, Snell described the development of bronchitis and bronchiolitis (103). He suggested the possibility that hypersensitivity, presumably to the polysaccharide portion of the endotoxin, was responsible. Cavagna et al. also described similar changes and again related them to a hypersensitivity mechanism, rather than to a primary toxic effect (25). These authors also demonstrated changes in lung mechanics, primarily an increase in airways resistance and tachypnea, after repeated, prolonged exposure. These studies postulate the possible implication of endotoxin inhalation in chronic obstructive pulmonary disease. They do not provide information on acute toxic effects. Single exposures to endotoxin in guinea pigs and hamsters were studied by Hudson et al. (59). They demonstrated polymorph recruitment into the airways, with platelet aggregations in small pulmonary vessels adjacent to bronchioles, and evidence of leukocyte diapedesis from blood to airways. Changes were not found in the alveoli.

There is a vast literature on the pathology and pathogenesis of changes which occur following intravenous administration of endotoxin. It is to this body of work that we must look for pathogenetic mechanisms, but with many reservations. There are several reasons for cautious extrapolation: It has already been noted that there is a considerable species variation in response; therefore, effects observed in animals may be irrelevant in man. Targets for endotoxin effects are numerous and complexly interrelated; targets hit and activated depend on the dose given. Effects produced by a big dose (e.g., diffuse intravascular coagulation) are not seen with smaller doses. To confound the dosage effect still more, preparations of endotoxins vary considerably in toxicity and sometimes in their ability to initiate some pathways of toxicity. For example, the ability to activate the complement pathway is dependent on molecular weight while some aspects of toxicity are not (45). As has been already noted, when administered by inhalation, endotoxin is, in order of magnitude, less toxic than when given parenterally. This suggests that accessibility to target sites is impaired when given by the respiratory route. Finally the complexity of responses to endotoxin and the interrelationships between multiple effector pathways make the determination of which is primary, secondary, or tertiary difficult to interpret.

There is considerable literature on the Shwartzman phenomenon (101). Basically this involves the "preparation" of a tissue (usually the skin) by local injection of endotoxin, followed several hours later by intravenous challenge. A

local hemorrhagic lesion results. Agents other than endotoxin can both "prepare" tissues and elicit similar reactions. Because this phenomenon seems to be unrelated to febrile illnesses induced by organic dusts, it is not considered further.

Endotoxin appears to be able to interact with any cell, possibly by virtue of the affinity of the hydrophobic portion of the complex for cell membranes (99). Earlier literature abounds with descriptions of necrosis of many tissues—gastrointestinal, reticuloendothelial, liver, heart, bone marrow, kidneys, and others when a large dosage of endotoxin is administered to animals (9). These gross changes are probably irrelevant in the context of the inhalation route of administration.

Target cells of greatest importance at lower doses are neutrophil polymorphs, platelets, endothelial cells, and possibly macrophages. Endotoxin also interacts with certain plasma proteins. It is able to activate the Hageman factor (clotting factor XII) and thereby has the potential to activate the blood clotting sequency and also the kallikreinkinin system (39). It is also able to activate the complement cascade, either the classical pathway (involving antibody reacting with determinants on the polysaccharide moeity) by the classical pathway in the absence of antibody via lipid A (29), or by directly activating C_3 in the absence of antibody [the alternate pathway of complement activation (47)]. The polysaccharide part of the molecule is responsible for alternate pathway activation (78). Complement activation by either pathway results in the production of C_3 and C_5 anaphylotoxins with their capacity to induce an acute inflammatory response via chemotaxis, lysosomal enzyme release, and the secretion of histamine from mast cells. Increases in serum histamine caused by endotoxin have been demonstrated *in vivo* (56) as have increases in serum lysozyme content (57). However, doubts as to the importance of the reactions of endotoxin with complement are raised by the work of Ulevitch and Cochrane. They showed that though prior depletion of C_3 in rabbits prevented the early reversible thrombocytopenia and hypotension on administration of endotoxin, the later phase of endotoxin effects and lethality were not influenced (113). These authors suggest the main effects of endotoxin are caused by the direct action of the lipopolysaccharide on peripheral blood cells, endothelial cells, and possibly other cells. Other work, using a similar approach, conflicts with this suggestion and implicates C_3 and terminal complement components in lethality (21). The studies of Johnson and Ward suggest that C_6 and possibly more terminal components, are protective against endotoxin induced lethality (60). There is still a need to define the role of complement activation in endotoxin-induced injury.

Platelets and granulocytes have a high affinity for lipopolysaccharide (105). Radio-labelled endotoxin given intravenously is rapidly bound, mainly to cells in the peripheral blood buffy coat and the liver (16)(17). Changes in the peripheral blood cells are usual in endotoxin effects. Within minutes of administration, a leukopenia is produced, followed several hours later by a leukocytosis mainly involving an increase in young polymorphs. A transient thrombocytopenia is also common and this can be followed again several hours later with a more prolonged fall in platelet count. The decrease in these blood cells is associated with their sequestration in the pulmonary blood vessels and in the sinusoids of the liver and spleen (4)(11). The mechanism causing this sequestration by the lung is not known but may involve effects of endotoxin on vascular endothelium (5). Ralis et al. also suggest that lysosomal enzyme release from granulocytes would produce lung injury. The doses they used were high (4 to 6 mg/kg); it is unlikely the extreme changes they describe would be produced by small quantities of inhaled endotoxin. Other workers have shown that endotoxin binds to endothelial cells (108), and that overt damage can result (46). This could initiate either blood clotting mechanisms, the release of agents such as prostocyclins which have been shown to be present in endothelial cells (66), or promote the attachment of peripheral blood cells.

Of major importance in the reaction of endotoxin with granulocytes is their release of endogenous pyrogen. As has been noted, fever is characteristically found in some species (including man) when endotoxin is administered. Much research has been devoted to investigating this phenomenon. The initial work of Beeson (7)(8) and Bennett(10) demonstrated the release of endogenous pyrogen, principally from granulocytes by endotoxin. This low molecular weight protein rapidly produces a monophasic rise in temperature without inducing leukocytosis. It is present in serum following administration of endotoxin and may be demonstrated by passive

transfer to other animals (4). Recently, endogenous pyrogens have been shown to be present in macrophages (51). The mechanism of endogenous pyrogen action is either directly or indirectly on the temperature regulating center of the hypothalamus. It has been suggested that prostoglandin E (PGE) may be released by endogenous pyrogen, and it is this substance which induces fever by action on the hypothalamus (102). In addition, prostoglandins of both E and F series have been shown to be released into the circulation in endotoxin shock (27)(62). It is, therefore, possible that release of PGE by endotoxin from any cell could contribute to the pyrexia without the intervention of endogenous pyrogen.

In addition to the prostoglandins, histamine, and bradykinin already mentioned, other vasoactive agents have been shown to be released by endotoxin. They include 5-hydroxytryptamine (3), catecholamines (84), cholinergic agents (115) and angiotensin (52). Whilst these agents may be important in endotoxin shock together with the possible direct effects of endotoxin on the heart and autonomic nervous system (55), their importance following the inhalation of small doses of endotoxin is debatable. Of this list of vasoactive substances, the prostoglandins may be the most important in relationship to the lungs. Parratt and Sturgiss provide good evidence to support this view (87). They pretreated cats with either a prostoglandin synthetase inhibitor or a prostoglandin antagonist and found that both the pulmonary and systemic hemodynamic effects of endotoxin were prevented. Their work also suggested neither histamine nor 5-hydroxytryptamine were of major importance in these effects. Additional research which supports the importance of the prostoglandins is the pyrogenicity of PGE (102). The observation that PGE is chemotactic to polymorphs (61) and that PGE given intravenously to human volunteers caused headache, an oppressive feeling in the chest, facial flushing, and abdominal cramps also suggests this group of lipids may be important in endotoxin-induced occupational fever. Prostoglandins of the F series also have potent effects. Thus, PGF_{2a} is a potent bronchoconstrictor (by inhalation in man) while PGE_2 is a bronchodilator (69). Fifteen-methyl-substituted PGF_{2a} has been administered as an abortifacient, and respiratory problems, a neutrophil leukocytosis, and a decreasing platelet count have all been observed (119). It is difficult to interpret the changes in neutrophils, as similar changes are observed during normal labor, however, many of the less serious effects of endotoxin administration can be mimicked by administration of these biologically active lipids.

A further effect of endotoxin which could be relevant to respiratory disease and possibly to the inhalent route of administration was shown by Shimizu and Mahour (100). They demonstrated a significant decrease in pulmonary surfactant, following a single intravenous dose of endotoxin in rabbits. Endotoxin could gain access to surfactant-producing cells in the peripheral airways by inhalation; thus this observation deserves to be pursued.

The other agents demonstrated to be released by endotoxin do have the capacity to produce pulmonary changes, particularly by effects on airways smooth muscle. Direct evidence to support this hypothesis, and indeed the role of prostoglandins in inhaled endotoxin effects is lacking. Studies of intravenous endotoxin effects reveal many possible pathogenic mechanisms which could theoretically operate when endotoxin is inhaled. Which, if any, are important is still unproven.

The phenomenon of tolerance to endotoxin pyrogenic effects was first observed by physicians using these agents for therapeutic purposes. Studies to investigate the mechanisms involved have been carried out in both animals and man. Earlier literature on tolerance is extensively reviewed by Bennett and Cluff (11) and Atkins (4). With daily injections, suitable animals species cease to give the expected temperature curve after about the fourth dose. Initially, there is a lengthening of the latent period and a decrease in the second fever peak. This is followed by a decrease, but often not the total disappearance, of the first fever peak. Other aspects of endotoxicity—lethality, shock, and leukopenia—are also diminished. It should be emphasized that tolerance is a relative state and a much larger dose of endotoxin will cause effects even in a tolerant animal. Tolerance persists in animals for about two weeks.

Tolerance in man is similar but has only been demonstrated by intravenous administration. Fever diminishes progressively and is usually absent or minimal by about the fifth or sixth daily dose. Tolerance is associated with a decrease and eventual absence of the unpleasant symptoms of endotoxin administration, although a

mild headache may persist. It should be noted that though the initial transient leukopenia does not occur in the tolerant human, subsequent leukocytosis is not prevented. The proportion of induced young polymorphs decreases, and the duration of the leukocytosis may decrease. Other blood changes noted in man include a transient decrease in mono-nuclear cells and in lymphocytes (42)(72)(75).

It is difficult to determine from the literature the precise length of time during which human tolerance persists after cessation of endotoxin administration. Morgan interrupted administration of endotoxin for up to five days with no decrease in tolerance, however, he showed that tolerant individuals again became sensitive between four and five weeks after the last dose (75). Interruption of the daily administration of endotoxin for two days had no effect on the progressive downward trend of pyrexia in studies reported by Mechanic (72). It is likely that the tolerant state persists in man for about two weeks.

Earlier studies into the involved mechanisms showed that tolerance to endotoxin obtained from one species of microorganisms would induce tolerance to an unrelated one (4). In addition, there appeared to be no correlation between specific circulating antibodies and tolerance; pyrogenic reactions could be induced when tolerance had disappeared even though antibodies persisted. This lack of correlation between agglutinating antibodies and tolerance was also shown to be the case in man (42)(75). An immune precipitate of antibody and endotoxin was shown to by pyrogenic to animals (74); passive transfer studies from tolerant rabbits produced only a mild degree of tolerance (41). All these studies tended to indicate that immunologic mechanisms were not involved in tolerance. The successful induction of tolerance in immuno-suppressed rabbits supports this view (31).

The work of Beeson provided an alternative mechanism (7)(8). He demonstrated that reticuloendothelial blockade, using thorotrast or trypan blue, would largely remove tolerance, and that these blockaded animals had retarded removal of endotoxin from circulation. He also showed that tolerant animals remove endotoxin from the blood more rapidly than nontolerant animals. He suggested that tolerance was due to an enhanced capacity of the reticuloendothelial system to remove and detoxify endotoxin. Other workers provided evidence to support this hypothesis. Biozzi et al. showed that endotoxin caused an initial nonspecific decrease in reticuloendothelial function followed by augmentation (12). Braude et al. using radiolabelled endotoxin, showed more rapid removal of the radioactivity from the circulation and increased uptake in the liver (18). Even in tolerant animals there was considerable binding of the radiolabelled endotoxin to peripheral blood cells. They noted, however, that even in animals which had spontaneously lost tolerance, the rate of endotoxin clearance from the circulation did not return to control levels. Following up this observation, Braude and Zalesky showed that smaller doses of endotoxin were cleared at equal rates in normally untolerant animals, thus casting doubt that augmented uptake by the reticuloendothelial system was important in tolerance at other than very high doses (18). Freeman further investigated the role of the reticuloendothelial system in tolerance (44). He noticed that the timing of changes in reticuloendothelial function did not agree with the changes in endotoxin response, and he was able to demonstrate the involvement of humoral factors in tolerance. However, these appeared not to be specific and he did not consider them to be immune in nature.

Other workers persisted in evaluating the possibility of immune mechanisms. The cross reactivity of tolerance was further investigated by Watson and Kim (117). They showed cross tolerance did occur between endotoxins obtained from some pairs of species and not between others. This is acceptable from an immunologic viewpoint because immunologic cross reactivity is common in bacteria. They also showed that tolerance induced by suspensions of lipid A cause only slight tolerance to the whole complex, while tolerance induced by the whole endotoxin molecule gave tolerance to lipid A. These investigators suggested that immune mechanisms were important in tolerance induction, but that the immunogenic determinant involved was not the somatic "O" antigen. It should be noted that it was antibody against just these determinants which had been measured in previous studies. In studies of rabbit tolerance, Greisman et al. provided evidence for two mechanisms: one could be abolished by reticuloendothelial blockade and was nonspecific; the second and more important, was humoral and endotoxin specific (49). The same group also investigated tolerance in man (5). They showed human tolerance to endotoxin

was not associated with increased reticuloendothelial activity as measured by the clearance of radiolabelled aggregated human serum albumen. They were also able to transfer tolerance using plasma and were able to break tolerance by giving half a dose to which the man was tolerant, followed by the other half two hours later. Radiolabelled endotoxin was also cleared more rapidly in tolerant subjects. These observations together with the fact that dermal reactivity to endotoxin was greater in tolerant than nontolerant volunteers (i.e., a hypersensitivity phenomenon) all suggest that an immune mechanism is involved in tolerance induction. The work of Kim and Watson supported this view with pig studies (63). They showed that colostrum deprived piglets were more sensitive than their colostrum fed litter mates and that the antibody responsible was probably in the IgM class. They also showed (in other species) that the specificity of the antibody was not against the somatic "O" antigens and that tolerance could be induced using endotoxin obtained from mutant organisms which did not posess "O" antigens. The evidence for antibody mediation of tolerance, therefore, seems sound. Differences of opinion expressed in the literature probably stem from the marked differences in dosage and purity of endotoxin preparations used, together with possible species variation.

Possible Effects of Mycotoxin Inhalation

Mycotoxins are toxic products produced by a wide variety of fungi. They vary greatly in chemistry, but the detailed structure of many of them is known. Major interest in mycotoxins has been in their ability to produce disease in animals and man when ingested. The classical poisoning of man by ergot alkaloids, produced by the fungus *Claviceps purpurea* growing on rye, is well known as is the carcinogenicity of aflatoxin B_1. Because, except under adverse conditions, man tries to avoid eating spoiled food, many of the mycotoxicoses have involved the poisoning of domestic animals. The toxicology of mycotoxins is thoroughly reviewed by Uraguchi and Yamazaki (114).

There is limited information on the effects of inhaled mycotoxin. Emanuel et al. (38) also citing Samsonov (95) suggested that the inhalation route may be important. They described ten patients who were exposed to massive fungal inhalation in silos. A pyrexial illness with chills, cough, and irritation of mucus membranes occurred with a latent period of several hours. Leukocytosis was common and chest x-ray changes suggesting diffuse interstitial disease were found in several patients. All recovered after an illness of from several days to a month. A biopsy of one patient's lung showed a multi-focal acute inflammatory process related to terminal bronchioles, alveoli, and interstitial tissue. These areas contained many fungal spores. The authors were unable to define which fungus was responsible, although they isolated at least five species. Because they could not demonstrate immunologic responses to any of a wide range of fungi and because the clinical picture was different from hypersensitivity pneumonitis, they ascribed the disease to fungal toxins.

There are no published accounts on the effects of mycotoxin inhalation in experimental animals. Unpublished studies from our laboratory (104) have investigated the effects of T_2 toxin given by the intratracheal route. T_2 toxin is a trichothecene toxin produced by *Fusarium* species which was one of the species of fungus isolated from the patient reported by Emanuel et al. No pulmonary pathology was induced by non-lethal doses of 50 and 100 μg. Destruction of rapidly dividing cells in the gastrointestinal, reticuloendothelial, lymphoid, and testicular tissue was, however, produced. More research is needed on the inhalation effects of this group of potent toxins.

CLINICAL DESCRIPTIONS

The symptomatology of the group of conditions included in this section are similar and will be considered together. After a latent period of from one to eight hours, the exposed individual develops a fever with chills, headache, myalgia, and general malaise. Respiratory tract irritation, with cough and chest discomfort, is common but not invariable; dyspnea is sometimes present. Sweating is often a feature; nausea, abdominal discomfort, and sometimes vomiting occur, particularly with polymer and metal fume exposure. The symptom complex lasts usually for up to 24 hours although the individual may feel unwell for a longer period of time. Pulmonary edema produced by fluorocarbon polymer fumes has taken about one week to resolve. If mycotoxins are accepted into this group, even longer is required for recovery. The intensity of reaction appears to depend on dose; a larger dose pro-

duces more severe effects with a shorter latency. This particularly applies to fluorocarbon polymer fumes. A sweet or metallic taste is often reported by individuals with metal fume fever.

Apart from pyrexia, physical signs are often completely absent in mild cases. In some patients, evidence of respiratory effects may be present in the form of moist sounds and occasionally rhonchi heard over the chest. There is sometimes evidence of mucosal irritation with redness of the conjunctivae and pharynx. Physical signs of pneumonia have been rarely reported following metal fume inhalation and pulmonary edema with polymer fume fever.

The disease is self-limiting. Moreover, repeated exposure may lead to a tolerant state. This is common in such conditions as mill fever for which endotoxin is considered responsible. Tolerance does occur to metal fume exposure, but symptoms of metal fume fever may recur if the individual is either exposed to a particularly high concentration or avoids exposure for a period of time. Tolerance to polymer fumes has not been clearly reported but probably does occur (see Epidemiology subsection). The effects of repeated exposure to high concentration of mycotoxins has not been studied.

There are no specific test for this group of diseases. Pulmonary function tests may be entirely normal or may reveal evidence of mild airways obstruction. Chest x-ray changes suggestive of pulmonary edema have been occasionally described in polymer and metal fume fever; changes suggestive of diffuse interstitial disease have been described following mycotoxin exposure. Otherwise, chest x-ray is usually normal. There is almost invariably a polymorph leukocytosis in the peripheral blood, usually with an increased proportion of young forms. Studies on polymorph airways recruitment in human airways are limited; it is possible this might provide a useful test. Fishburn and Zenz suggested measurement of the pulmonary fraction of lactic dehydrogenase could be useful in metal fume fever (43). This has not be confirmed.

There is no specific therapy for this group of diseases; in most situations, after overnight bed rest a patient will be recovered. Aspirin is useful because of its antipyretic and analgesic actions. Other more unusual complications such as pulmonary edema should be treated by appropriate methods. The acute disease invariably recovers, however, chronic toxic effects do occur with some of the agents, e.g., cadmium. These can clearly carry a totally different prognosis from those of the acute disease, but consideration of long term effects is not within the scope of this section.

DIAGNOSTIC CRITERIA

There are no specific diagnostic criteria for this group of occupational fevers. The key to their recognition is physician awareness of their existence and the taking of a careful and detailed occupational history. Symptomatology is similar to that of many virus infections from which they need to be differentiated. Unless virus isolation or serology are carried out, there are no specific ways in which they can be differentiated. The results of virus isolation or serology are slow and reliance must be placed on clinical judgment. Helpful points in differentiation are that virus infections are usually longer lasting; often produce greater evidence of respiratory tract damage than occupational fever; and may not be associated with a polymorph leukocytosis, at least in the early stages.

METHODS OF PREVENTION

The prime method is the prevention or limitation of exposure to fumes and dusts which cause the febrile reactions described. This should be achieved primarily by engineering controls with adequate exhaust ventilation directed toward the source of the agent. This is particularly relevant in welding and cutting operations in confined spaces. Respirator use should be limited to temporary situations where high concentrations of an agent are inevitable. Adequate housekeeping of a plant will minimize exposure. Polymer fume fever has been frequently related to the smoking of contaminated cigarettes. This source can be avoided by forbidding smoking in risk areas and the provision of facilities for adequate personal hygiene before the worker leaves such areas. Environmental standards recommended by NIOSH are largely based on chronic effects; dose-response data is lacking with respect to pyrexial reactions. It is, however, likely that with respect to metal fumes and cotton dust, recommended standards will prevent or considerably minimize febrile reactions. Because of their complexity, NIOSH has not considered environmental standards for the breakdown products of fluorocarbon polymers to be practical; reliance has instead been placed on good work practices

and engineering controls. It is probable that the current OSHA standards for grain dust which is grouped as a "nuisance dust" is not sufficiently low to prevent grain fever. There is need for reconsideration of this standard.

RESEARCH NEEDS

There are four major gaps in our knowledge relating to this group of conditions: what is the responsible agent within the complexity of the fume or dust; how does it induce fever; what are the dose-response relationships in previously unexposed individuals and in repeatedly exposed workers; and are any currently unrecognized long-term effects induced. Even metal fumes contain several metals and which is responsible for pyrexial illness is in many cases not known. Organic dusts from cotton or grain are incredibly complex and variable and it is only by inference that microbial toxins are considered to be important. These research gaps will be very difficult and costly to close and because of the nature of the conditions involved, will inevitably have a low priority for funding.

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