Effects of Single and Repeated Exposures of Humans and Rats to Vinyl Chloride

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Rats exposed eight hours daily to vinyl chloride at concentrations of 2% for three months and 5% for 19 days exhibited changes in liver and spleen weight and in red and white cell counts. Except in the case of liver, tissue alterations did not accompany these changes. The alterations in liver morphology were within the normal range and were not pathologic in character. Because other facets of the animals' response, such as rate of growth, serum transaminase and hemoglobin, were unchanged, it is suggested that the present threshold limit value of 0.05% need not be lowered.

Introduction

THE TOXICITY of vinyl chloride has been reviewed recently.[1,2,3] Because the threshold limit value of 500 ppm is based on limited data[4] using vinyl chloride less pure than that now obtainable[5] the effects of acute exposure in man and rats and long term exposure in rats was investigated by us in 1959 and is described here. Our data do not support the conclusion of Torkelson, *et al.*[3] that the threshold limit value should be reduced ten-fold; indeed their data indicate a need for further studies prior to any revision of the threshold limit value.

Material

The vinyl chloride monomer was supplied by the Perkins Plant of Solway Process Division, Allied Chemical Corporation, in four 100 lb. cylinders with the characteristics shown in Table I, presumably differing materially from the vinyl chloride used by Torkelson, *et al.*[3] only in the presence of 60 ppm of the inhibitor, phenol. Gas chromatography of the liquid phase indicated the presence of more than 99% vinyl chloride, together with a trace of air and carbon dioxide.

TABLE I
Analysis of Vinyl Chloride Monomer

Acid	2.2 ppm
Acetylene	0.0
Aldehyde	1.9 ppm
Iron	0.0
Sulfur	0.0
Phenol	60 ppm
Non. Vol.	11 ppm
Water	170 ppm
Color	w.w
Assay	99+%

Methods

Experimental

Desired concentrations were obtained by metering air and vinyl chloride through flowmeters calibrated for these gases and passing the appropriate flows through a 2-liter mixing chamber. The concentration was also continuously monitored by a thermal conductivity meter calibrated for vinyl chloride versus air. The desired concentration of vinyl chloride was maintained with less than 5% deviation. The total gas flow was about 50 liters per minute (lpm) in all but one of the experiments.

Five experiments were conducted: (1) a five-minute exposure of human beings to concentrations of vinyl chloride ranging from 0.0 to 2.0%; (2) an exposure of rats (Sherman strain rats from Rockland Farm, New City, N. Y.) for as long as two hours with concentrations up to 15%; and (3, 4, and 5)

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exposures of rats to concentrations of 8 to 10% for 15 days, 5% for 19 consecutive days and 2% for 92 days.

Pathological

The experimental and control animals were killed by ether inhalation after exposures to 2, 5 and 8 to 10% vinyl chloride were completed. Each animal was autopsied according to standard practice. In addition to the gross examination of all animals, all the livers, kidneys and spleens were examined microscopically and some animals received a complete microscopic examination. Heart, lung, liver, spleen, urinary bladder, testes, prostate, ovary, brain, spinal cord, pituitary, tibia, pancreas, stomach, small and large intestine, adrenals, kidneys, uterus, fallopian tubes, thymus, thyroid, parathyroid, eye, knee joint, bone marrow, skeletal muscle, salivary glands and skin were removed from each animal and preserved in 10% buffered formalin. All tissues were examined grossly both at autopsy and after formalin fixation. Following fixation, representative samples of all tissues were processed according to standard histological procedure and stained with hematoxylin and eosin; separate specimens of liver were stained for fat with the *Flaming Red* technique. The animals receiving such a complete examination of the tissues listed included two males and one female rat that had been exposed 15 times and one female rat exposed ten times to the 8 to 10% level; eight experimental and nine control animals surviving the 5% exposure; and 20 randomly selected rats, equally divided as to experimental and control groups and to sex, exposed to 2% vinyl chloride.

The marked increases in liver weight accompanying the exposures to 2% and 5% of the gas, the decrease in spleen weight in the 2% exposure and the reported kidney changes in exposure to 500 ppm[3] led us to examine these particular tissues with a blind technique, thus excluding the operation of any bias or prejudice from the judgments. All slides, including duplicates, were randomly numbered so that it was impossible to distinguish, without the code, which had been experimental and which control. The slides of the liver, spleen, and kidney were examined and classified, then recoded and re-examined; in this manner a measure of the consistence and reliability of the pathologist's technique was obtained. This consistency was nearly perfect in the case of liver slides, and only slightly less so for spleen and kidney. The results of these examinations are reported in the appropriate following sections.

Results

Experiment 1

Because the main objective was the determination of the effect of long term exposure to vinyl chloride, the maximum concentration of the gas to which humans might conceivably be exposed without any immediate acute effects was determined; this concentration then became the basis for determining the concentration used during the 92-day exposure of rats.

Three men (26, 35, 50 years; 86, 78, 73 Kg.) and three women (25, 40, 55 years; 64, 52, 61 Kg.) were exposed twice each day, separated by a 6-hour interval, for three successive days to six different concentrations of vinyl chloride: 0.0, 0.4, 0.8, 1.2, 1.6 and 2.0%. The concentrations were presented in a different order to each subject to make it possible to factor out any possible adaptation to either the gas or the experimental situation; the 0.0% concentration was included so that some assessment of suggestibility could be made.

Until its conclusion, the subjects were told neither the effects to expect from the exposure nor the purpose of the experiment; nor was information vouchsafed as to the concentrations that were used at any time. The subjects each sat in a chair separated from the gas mixing equipment by a screen, a simple plastic breathing mask affixed over the face, covering the mouth and nose. The rate of air or air-gas mixture passed through the mask was sufficient (50 lpm) to prevent any dilution effects from the atmosphere. After five minutes of breathing the mixture, the exposure was terminated and the subjects were asked to compare their feelings at this time to the time immediately

prior to putting on the mask; no suggestions of any kind were made. The responses of the subjects are summarized in Table II. It is apparent that the maximum concentration causing no effect in any subject lies between 0.8 and 1.2%. From the responses it is evident that vinyl chloride causes clear-cut intoxicating symptoms which can serve as adequate warning signs of its presence.

TABLE II
Responses of Human Subjects to Varying Concentrations of Vinyl Chloride

Per Cent Concentration	Response
0.0	No differences reported by Subjects 1, 2, 4, 5 and 6. Subject 3: "slightly dizzy".
0.4	No differences reported by *all* subjects.
0.8	No differences reported by Subjects 1, 2, 4, 5 and 6. *Subject 3: "slightly heady".*
1.2	No differences reported by Subjects 1, 3, 4 and 5. Subject 2 unsure, somewhat dizzy in middle of exposure. Subject 6, reeling, swimming head, "just like getting gas".
1.6	No effect reported by Subject 5. All others report various degrees of intoxication with dizziness, lightheadedness, some nausea, dulling of visual and auditory cues; these *symptoms disappeared rapidly upon* termination of the exposure.
2.0	All subjects reported intoxicating effects. Subject 1 reporting a headache that persisted for 30 minutes. These symptoms appeared earlier in the exposure than at 1.6% and the symptoms were more intense than at 1.6%.

Experiment 2

To gain further insight into the intoxicating effects of vinyl chloride rats were exposed to varying concentrations of vinyl chloride for periods up to two hours. The effluent gas from the mixing chamber, at the desired concentration, was passed through a 10-liter all-glass exposure chamber containing two rats. At a 5% concentration intoxication is moderate but the righting reflex is lost; intoxication is more intense at 6% but the righting reflex is still present. This reflex is lost at a concentration of 7%; the corneal reflex disappears at a concentration of 10%. On removal from the chamber, the animals return to the pre-exposure state rapidly. One animal was sacrificed after exposure to the 10% concentration and showed no visible gross pathology. Exposure to a concentration of 15% resulted in deep anesthesia within five minutes. Effusion of fluid from the mouth preceded respiratory failure in one rat after 42 minutes; autopsy revealed edema and congestion of the lungs. The second rat was maintained under this deep anesthesia for two hours; on removal to air, there was an uneventful and prompt recovery.

Experiment 3

Some notion of the distinctive and specific pathology that might be caused by vinyl chloride was our object in exposing rats to a concentration of 10%.

Thirty-six rats, equally divided as to sex, were divided randomly into an experimental and a control group; the 18 experimental rats were exposed to the gas in a 1100-liter steel chamber. The concentration was initially raised rapidly to the desired level by admitting vinyl chloride without admixture with air until the effluent from the chamber attained the desired level as noted on the thermal conductivity meter. A fan within the chamber, connected by a flexible cable to an electric motor outside of the chamber (thus avoiding the hazard of an explosion), mixed the vinyl chloride with the air within the chamber. Thereafter, the effluent from the 2-liter mixing vessel was admitted to the chamber; to conserve gas, the throughput of this highest concentration was 20 lpm.

The experimental rats were exposed daily from 0830 to 1630 hours while the control animals were exposed from 0000 to 0800 hours. At this concentration, as already noted, rats lose consciousness, regaining it five to ten minutes after removal to air. After two consecutive 8-hour exposures, however, the appearance of the animals suggested that there would be no survivors if this concentration were maintained for the contemplated 15-day period; consequently, beginning with the third exposure, the concentration was reduced to 8%. The test was interrupted for one day after the seventh daily exposure because of a mechanical breakdown. Of the group exposed in this fashion, three female rats died, after the second, fifth and fourteenth exposures; the two animals that died earliest were replaced with substitutes for the remaining exposure period; eight female rats were thus alive at the end of the fifteenth exposure. Female rats exposed 10 and 15 times were autopsied

TABLE III
Classification of Morphologic Changes in Livers

Class	Description
1	No swelling, no vacuoles, sinusoids visible.
2	Slight swelling of cells, only a few faint vacuoles or none, sinusoids visible but compressed.
3	Moderate swelling of cells, most cells with definite fine to medium vacuoles, sinusoids compressed.
4	Marked swelling of cells, large irregular "vacuoles" or clear spaces, compression of sinusoids. Changes focal in distribution.
5	Similar to 4 but changes more widespread and diffuse.

TABLE IV
Classification of Morphologic Changes in Kidneys

Class	Description
1	Cells well preserved, no vacuoles, glomeruli normal.
2	Vacuolization and "pyknosis" of some collecting tubules. Otherwise as 1.
3	As 2 but with more extensive vacuolization and "pyknosis" including proximal collecting tubules in cortex.
4	As 3 but with vacuolization and "pyknosis" extending to convoluted tubules.

at the termination of the exposure; the remaining six rats were autopsied 15 days later, five of these rats having been exposed 15 times and the sixth rat 13 times. The mortality was greater among the male rats: only two males survived 15 exposures, the remaining males, and their replacements, surviving only an average of eight exposures. The two male rats exposed 15 times were autopsied at the termination of the exposure.

There was no weight gain in the initial days of the exposure to this concentration, although after the ninth day some resumption of growth seemed to occur, possibly an indication of the development of tolerance to the effects of the gas as the exposure continued. Upon termination of the exposure, growth resumed promptly at the same rate as the control animals. Both at the 16th and at the 30th days, there appeared to be no differences in liver: body weight ratios between experimental and control rats, although too few livers were weighed at the termination of the experiment to make meaningful comparisons of this ratio.

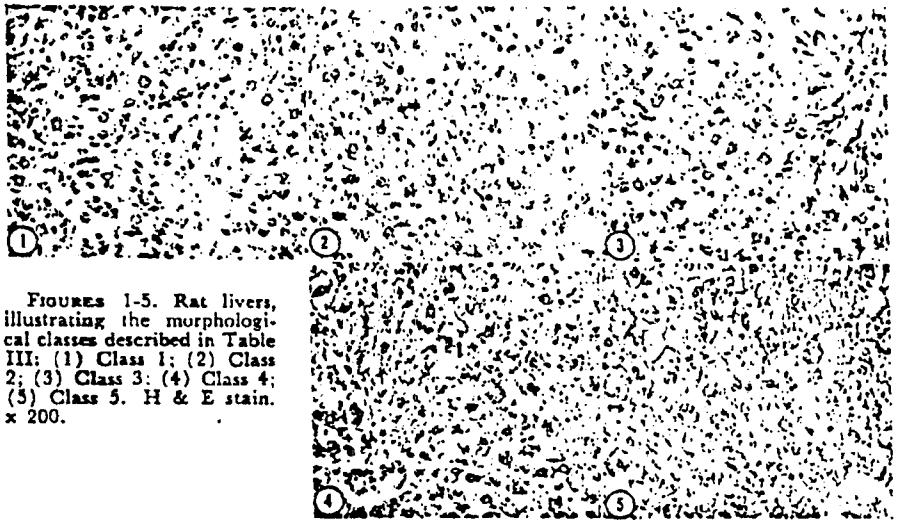
The external appearance, coat and tail, of all the animals was within normal limits. About a third of the animals had parasitic liver cysts. No differences in appearance, color, consistency or degree of congestion were observed between the livers of experimental and control animals. The lungs of three experimental animals sacrificed immediately upon cessation of the exposure had numerous focal fibrinous pleural exudates overlaying nodular yellow-brown parenchymal lesions which had the appearance of regions of acute necrotizing focal pneumonia. Of the six experimental animals sacrificed two weeks after the exposure, the lungs of two revealed a few adherent fibrous pleural adhesions which were interpreted as representing regions of healed pneumonia. All other organs and tissues were within normal limits, with no differences between experimental and control animals.

The experimental animals sacrificed at the termination of the exposure received a complete histologic examination. The lesions in the lungs of the three animals in this group showing gross pleural pathology were seen to be due to acute focal necrotizing pneumonia in varying stages of organization. Some pulmonary edema was present as well as diffuse infiltrates of mononuclear cells in the alveolar septae. Some areas of metaplasia were present in and near the regions of pneumonia and were interpreted as secondary to the pneumonia.

The parasitic liver cysts seen grossly were confirmed microscopically. The liver sections stained for fat revealed individual variation of some degree but no significant deviation from normal. The coded slides of the livers were classed according to the descriptions in Table III while kidney and spleen were judged according to the criteria in Tables IV and V; Figures 1, 2, 3, 4, and 5 are

TABLE V
Classification of Morphologic Changes in Spleen

Class	Description
1	Average size follicles, little or no congestion, balance between lymphocytes, germinal epithelium and interstitial tissue.
2	Obvious congestion, no change in follicles or epithelium, volume of germinal centers less than volume of peripheral lymphocytes.
3	Germinal centers approximately same volume as peripheral lymphocytes, moderate congestion.
4	Increased number of lymphocytes, hyperplasia of germinal centers (greater than volume of peripheral lymphocytes).
5	Active hyperplasia: 2 classes of lymphocytes, (1) a zone immediately around germinal centers containing young lymphocytes surrounded by (2) a peripheral zone of small dark lymphocytes.
6	Lymphocytic hyperplasia extending to include most of the interstitium.



FIGURES 1-5. Rat livers, illustrating the morphological classes described in Table III: (1) Class 1; (2) Class 2; (3) Class 3; (4) Class 4; (5) Class 5. H & E stain. x 200.

illustrative of the class descriptions in Table III. There were no significant differences in the scoring of the groups, although there was a class "5" and no class "3" in the rats killed at the termination of the exposure, whereas there were no livers in class "5" among the control animals. There were no class "5" livers among the experimental rats killed two weeks after the exposure; the slides were evenly divided between scores of 3 and 4.

Kidney slides from the experimental animals were not graded differently than from the controls but all spleen slides from experimental animals received the highest score, differing significantly from the control spleens, although some controls also received such high scores.

Experiment 4

These preliminary tests seemed to indicate that vinyl chloride was an anesthetic gas which might also act as a lung irritant. In order to assess this feature of its action, to highlight significant pathological features and to avoid the potentiality of damage arising from anesthesia alone, five female and five male rats, matched with controls, were exposed for eight hours daily to five per cent vinyl chloride in air for 19 consecutive days. The experimental animals were placed within the chamber at 0830 and removed at 1630 and the control animals from 0000 to 0800 hours. To prevent contamination of food or water, both groups of animals were placed within the chamber in empty cages; hence experimental and control animals were deprived of food and water for eight hours daily. The requisite concentration of the vinyl chloride was attained initially as in Experiment 3, but the chamber was ventilated at 50 lpm.

Although the body weight of the experimental rats decreased initially, this trend was reversed by the fourth exposure, the rate of growth thereafter being no different than the controls. The drop in weight at the start and the subsequent resumption of growth was paralleled by an apparent increasing tolerance to the gas as the exposures continued. At the start, the intoxication of the rats was marked, instability of the hind legs being a prominent feature of the exposure. With each exposure, however, there was an obvious diminution of these symptoms, so that by the fifth or sixth exposure, it was not possible to distinguish any evident symptoms of neurological deficit.

Hemoglobin determinations during the ex-

ology being evident in either experimental or control animals.

The parasitic liver cysts seen grossly were confirmed microscopically. Liver sections stained for fat revealed normal variation, but no animals had increased intracellular fat nor were there differences between the experimental and control animals. Graded in accord with the morphology in Table III, the liver slides revealed differences between the groups. The mean score of the control group was 1.58, that of the experimental group 3.63. No liver in the control group scored more than 2 and none in the experimental group scored less than 3; one liver scored 5. Because there was no overlap the differences between the means are highly significant.

There were no differences in score for the spleens in the two groups, but the kidney slides of the experimental animals scored significantly less than their controls.

Discussion

The data from the present investigation confirm the acute effects to be expected from various concentrations of vinyl chloride: concentrations below 1%, when exposure is limited to five minutes, cause no observable intoxicating effects; five minutes, however, is shorter than the time necessary to reach an equilibrium level in the circulation; from behavioral observations in the rat, it may be estimated that in five minutes some two-thirds of the equilibrium level is reached; consequently a concentration of 0.6 to 0.7%, if long continued would not produce intoxication. As the concentration rises above this level the intensity of the intoxicating signs increases until at a concentration of 7% the righting reflex is lost; at 10% the corneal reflex disappears and at concentrations of 15% and above respiratory failure takes place. Vinyl chloride thus acts as an anesthetic gas, its depressant action increasing with increasing concentration of the gas in the air breathed, the corresponding increasing neurological deficits ending in death at concentrations greater than 15%. The purpose in exposing rats to concentrations causing anesthesia (8 to 10%) was an attempt to produce some singular or characteristic pathology. It cannot be said that this goal was achieved, the results being questionable and uncertain. Lung lesions were certainly present but these could not be ascribed with certainty to any irritant properties of the gas since they might well have arisen from the long-continued anesthesia; there was an apparent regression of these lesions in rats allowed a 14-day recovery period. The presence of pneumonia certainly raises the possibility of an acute toxic effect on lung tissue at these concentrations; however, the pneumonia could just as well be caused by secondary infection during the severe central nervous system and respiratory depression, an interpretation favored somewhat by the diffuse lesions and by the irregular occurrence of the pneumonia.

The kidney and liver changes described by Mastromatteo, *et al.*[2] in rats exposed for 30 minutes to 20, 30 and 40% of vinyl chloride, were not observed here, although 15 repeated 8-hour exposures to an anesthetic concentration is also a relatively severe stimulus. The findings in the lungs agree with the relative lack of effect found by Mastromatteo *et al.* in rats exposed for 30 minutes to 10% vinyl chloride, except that continued exposure, for days, does result in mortality. The relative lack of pathology as the result of 30 minute exposure at 10% found by Mastromatteo *et al.* would seem to support the view that lung lesions found after repeated exposures could well arise from the anesthesia and not from some action peculiar to vinyl chloride. There was no indication at either the 2% or 5% level of any untoward or other effects upon the lung tissue.

As an overall measure of general health, body weight and rate of growth are sensitive indicants. Even in the exposure to a concentration of 5%, which at first produces a marked and severe intoxication, the sharp drop in the weight of male experimental animals seen at the start of the exposure was soon reversed so that by the end of the 19-day exposure there was no difference between experimental and control rats of either sex. Body weight and rate of growth similarly showed no differences between the

groups in the 2% exposure. It must be emphasized again that the growth of the rats during the 5% exposure support the observation of the rat's behavior which indicated that there was a rapid development of tolerance to the intoxicating effects of this concentration.

Neither the 2% nor the 5% concentrations caused changes in the prothrombin time, hematocrit or hemoglobin values. At both the 2% and the 5% concentrations, the white cell count was lowered significantly, although still well within the normal range. The increase in red cells, although significantly elevated in the 5% exposure, was not correlated with changes in the hemoglobin content. The increase in concentration of the vinyl chloride is associated with a greater fall in the white cells and a greater (and significant) increase in the red cells at the 5% level. Although lymphocytes and neutrophils are increased, only the change at the 2% concentration unlike the previous cell changes, reaches the statistically significant level. It is difficult to know if these changes have any toxic significance, since no tissue changes were seen upon microscopic examination that would account or be associated with a drop in the white cells or an increase in red cells. The decrease in spleen: body weight ratio is in a direction opposite to that usually associated with a severe drop in white cells; although the white cell count did not suffer a severe drop, the decrease was substantial at the termination of the exposure.

The only finding suggesting a specific toxic action of vinyl chloride is the increase in liver weight on exposure to 5% for 19 days and to 2% over 92 days. The increase in liver weight is not only highly significant statistically but is also substantial, amounting to a 30% increase over the controls. It is unfortunate that no information is available as to whether this increase is reversed on discontinuing the exposure. The increase in liver weight may be interpreted as indicating alterations in water, electrolytes and protein content of the liver parenchyma, but that such changes presage the development of actual histologic lesions is not certain in view of the wide range that the liver: body weight ratio may encompass (Table VII). Rather this increase may signify a non-specific response to metabolic derangements occasioned by mild and moderate intoxication for daily 8-hour periods. From the data obtained here, it is not certain that histopathological change would have occurred had exposures been carried out for longer times.

In the paper by Torkelson *et al.*, histopathological changes in the liver and increased liver:body weight ratios are reported in male rats exposed to 500 ppm vinyl chloride for 4.5 months. That there is no causal relation between the reported histopathology and the increases in liver:body weight ratio is evident from the extensive data gathered by these investigators. Female rats exposed to 500 ppm vinyl chloride for 4.5 months showed no statistically significant increase in liver weight but are reported to have histopathological changes in the liver. Female rats exposed to lower concentrations (100 and 200 ppm) for six months had significantly increased liver:body weight ratios but no pathology. On the other hand, rabbits of both sexes exhibited liver pathology without showing any increase in liver weight after exposure for six months to a concentration of 200 ppm. The authors correctly point out that organ:body weight ratios may well be artefactual, illustrating the point by the significant decrease in kidney weight found in female rats exposed to 50 ppm for six months; such rats exhibited no changes when exposed to higher concentrations. By the same token, but overlooked by the authors, the increased liver:body weight ratio in female rats at 100 and 200 ppm is with equal reason artefact because no statistically significant increase occurred at 500 ppm. Apparently, also, species differences are of importance in the reactivity to vinyl chloride, male guinea pigs suffering a significant *decrease* in their liver:body weight ratio when exposed to 100 ppm for six months.

There are six possible combinations of the presence or absence of pathology and increases, decreases and no change in liver weight. The one combination not observed

by Torkelson, *et al.* is histopathological change associated with a decrease in liver weight. Obviously, if five of the six possible combinations have been observed in a relatively small sample, no causal connection can be said to exist between these two measures.

Changes in the liver:body weight ratio may well have some toxic significance, but if they are unaccompanied by histopathological alterations, increased fat content or serum transaminase changes it is impossible to conclude that taken alone they signify much. Reference to Table VII will show that the liver:body weight ratios of the rats used as control animals in the 5% exposure were significantly higher than the experimental animals in the 2% exposure. This illustrates well the fact that though control animals are used, unknown and non-specific changes in the environment, time of the year, temperature, diet, etc., may be responsible for changes in organ:body weight ratio without at the same time producing pathological alterations in the organ.

Similar considerations apply to the decrease in spleen weight; here, not only was pathology not observed, but there was no difference in the morphological character at either the 2% or 5% level between the experimental and control groups.

Unlike the interstitial and tubular changes in kidneys of rats exposed to 500 ppm of vinyl chloride reported by Torkelson, *et al.*, was the lack of any pathology in our animals exposed to 2% and 5% and the fact that the only morphological alteration in which a significant difference between control and experimental animals occurred (kidney at 2%) indicated that the control animals were further from "normal". Because it is unreasonable to attach toxic significance to changes associated with a control air exposure, it is our belief that the morphological alterations we have observed should not be interpreted as manifestations of pathology.

The concentrations to which the rats were subjected in these experiments were at least 40 times those used by Torkelson, *et al.* If any reliance is to be placed in a dose-effect relationship, pathology of some considerable degree should have been found in our experiments. Yet only morphological alterations of the character already described and pictured were seen, which, in our knowledge and experience, are of no pathological significance. Whether the explanation resides in a difference between the rat strains used by us and by Torkelson *et al.* or elsewhere is not known, but without additional data it is impossible to resolve the contradiction.

On the basis of the present data, and the seeming unimportance of the liver weight changes seen by Torkelson *et al.*, and without further evidence, a change of the present threshold limit value of 500 ppm seems unwarranted.

Summary

From 5-minute exposures of human subjects to concentrations of vinyl chloride ranging from 0.0 to 2.0%, it is estimated that a prolonged exposure to a level of more than 0.6% is necessary to produce minimum symptoms of intoxication. Rats exposed for up to two hours to higher concentrations exhibited moderate intoxication at 5%, lost their righting reflex at 7% and the corneal reflex at 10%. Respiratory failure occurred at 15%. If the exposure to 10% was long continued (two 8-hour daily exposures), mortality increased; death was apparently caused by a pneumonic process, but it was impossible to decide whether this was the result of a primary action or secondary to the anethesia.

Rats exposed eight hours daily to 5% for 19 days or to 2% over 92 days did not show any lung involvement. These levels had no effects upon growth rate, hemoglobin, hematocrit or prothrombin time. At both concentrations there were increases in the liver: body weight ratio and decreases in the white cells; at 2% the spleen:body weight ratio decreased and at 5% there was an increase in red cells.

No gross or microscopic changes were found in any tissue that was correlated with

the changes in the formed elements of the blood. The increases in liver:body weight ratios were associated with morphological alterations in the liver which appeared to have no pathological significance, while no meaningful morphological alterations were evident in either kidneys or spleens.

Because, in the long term exposures, it was impossible to attach any toxic significance to the changes noted or to observe any histopathology, and because other aspects of the animals' reactions, such as growth rate, were unimpaired, the presently accepted threshold limit value of 500 ppm for vinyl chloride, one-fortieth of the concentration tested here, seems to offer an adequate margin of safety for human exposure.

Acknowledgment

It is a pleasure to acknowledge the technical assistance of Malcolm Nicholson, Frederick A. Putt and Miss Lillemor Wallmark.

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Sources and Use of Toxicological Information

The New York University Medical Center in cooperation with the American Industrial Hygiene Association will present a course on *Sources and Use of Toxicological Information.* The course will be given October 14-18, 1963, at the Onchiota Conference Center, Sterling Forest, Tuxedo, New York.

The course is designed to acquaint those concerned with advanced methods of securing and interpreting pertinent toxicological information. Application and principles will be stressed rather than details of experimental toxicology. The design of the course eliminates the need for specialized scientific background so that all administrative and technical persons having responsibilities for use of toxicological information can benefit. Guest lecturers who are specialists in selected fields will supplement the staff of N.Y.U. Institute of Industrial Medicine for presentation of the subject material. Areas to be covered are: biological principles involved, sources of toxicological information, applications to in-plant problems, Federal regulations, and requirements of various agencies.

Inquiries and registrations should be directed to New York University Medical Center, Institute of Industrial Medicine, 550 First Avenue, New York 16, New York. The registration fee is $150 with a deposit of $25 required. Accommodations (double occupancy) at the Onchiota Conference Center for the evening (dinner) October 13 through lunch October 18 are available at $21 per day including meals (payable to the Center on departure).

Documentation of the Threshold Limit Value
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VINYL CHLORIDE

$CH_2{=}CHCl$

200 ppm (Approximately 770 mg/m^3)

Vinyl chloride is a flammable gas with anesthetic properties at high concentrations. At anesthetic concentrations (8 to 12%) it has serious effects on cardiac muscle resulting in arrythmias and sensitization in dogs(1,2). There is a wide margin between anesthetic and lethal concentrations (30-40%)(3). Torkelson, Oyen and Rowe(4) reported that repeated seven-hour exposures for six months at 200 ppm resulted in histologic changes in the central lobular region of the livers of rabbits, but not in rats, guinea pigs and dogs. At 100 ppm there was only slight liver enlargement. A subsequent report by Lester, Greenberg and Adams(5) on the effects of repeated exposure of rats to vinyl chloride assaying 99 + percent purity at 2 and 5% concentration stated that, although liver changes were noted, they were not considered to be of pathological significance. In their opinion, a recommended TLV of 500 ppm was satisfactory for worker exposure.

An interim report was made by Mutchler and Kramer(6) of long industrial health experience with vinyl chloride workers. Beginning in 1950, continuous monitoring was begun at five or six stations and the results compared with breath analyses(7) for vinyl chloride for 50 workers. Between 1950 and 1967 the mean air concentration was 160 ppm, with one maximal peak at 600 ppm of vinyl chloride and with great daily variation from 30 to 170 ppm, on the average. During part of this time vinylidene chloride* was an associated air contaminant estimated at around 5 ppm. Twenty-one clinical parameters were measured for comparison with the environmental data, and relationships were obtained by stepwise multiple linear regression analysis. Of medical examinations numbering 404 on 97 workers, 66 were used for comparison with 650 controls. These examinations with final diagnoses made according to the international classification of diseases, failed to reveal any overt condition attributable to vinyl chloride (or vinylidene chloride) exposure. No differences of physiologic significance were found in blood pressure, hemoglobin, electrocardiograms, and no body abnormalities (acro-osteolysis) appeared. No one was clinically ill. Six clinical parameters appeared to be altered, however. Among these, beta lipoprotein, icterus index, and bromosulfalein retention time may have some physiologic significance. The investigators felt, from a review of the interim findings, that a time-weighted average exposure concentration at 300 ppm (combined vinyl chloride and 5 ppm vinylidene chloride) could result in some degree of liver dysfunction. The multiphasic screening tests are continuing on all exposed workers, and analysis of the findings is being made on an individual worker basis. In the meantime, a time-weighted average threshold limit value of 200 ppm vinyl chloride (with a few ppm vinylidene chloride) seems appropriate to prevent adverse systemic effects from long-continued daily exposure.

(* A 90-day animal inhalation exposure to vinylidene chloride at 5 ppm was without observable effect.)

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The Correlation of Clinical and Environmental Measurements for Workers Exposed to Vinyl Chloride

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A method is described for the statistical consolidation and correlation of environmental measurements and clinical findings using as an example a group of healthy male workers exposed routinely to vinyl chloride for periods up to 25 years. Retrospective in nature the study reveals several statistically significant effects from chronic exposures to vinyl chloride and traces of vinylidene chloride.

Introduction

For validating an industrial hygiene standard, it is essential to perform careful and comprehensive studies of the possible effects of substances on exposed workmen. In practice, however, very few substances have been the object of sufficient study to furnish reliable guidelines. Today, specialists in occupational health must recognize the need to develop programs which will better identify the relation between stresses acting on the human body in the work environment and physical changes that can be measured clinically, to explain the significance of these changes and use the results to help refine our guidelines for environmental control.

Although toxicologists are constantly predicting what exposures are likely to be safe for people, there will always be some doubt about their predictions until enough human experience has been gained to prove their accuracy. The "proof of the pudding" should result from the correlation of good environmental measurements with the results of a well planned medical surveillance program. It is likely that such feedback from human experience will differ from the animal experimental data in that it will not define a level of exposure which will actually cause injury, at least frank injury. However, except in cases where an industrial hygiene standard has not been applied, the feedback from human experience could be expected to describe levels of exposure which have been shown to be either acceptable or marginally unacceptable. This information would be valuable to toxicologists because it would strengthen their skills in predicting from experimental animal data effects of substances on humans. In a broader sense, it would be useful in substantiating criteria to be used for industrial hygiene standards.

For several years The Dow Chemical Company's medical and environmental health groups have been conducting concurrent medical and environmental surveillance of a large worker population exposed to many different chemicals. The project described in this paper analyzes the information already gained from concurrent surveillance and relates it to the determination of acceptable levels of exposure. A method is described for the statistical consolidation and correlation of environmental measurements and clinical findings, using as an example a group of 98 healthy male workers who had been exposed routinely to vinyl chloride for periods up to 25 years. Retrospective in nature, the study reveals several statistically significant clinical changes due to chronic exposures to vinyl chloride and smaller amounts of vinylidene chloride. By isolating these apparent effects and examining them in the light of our medical interpretation, we have developed what appears to be a promising technique for

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relating clinical information to worker exposures to achieve a more refined industrial hygiene standard.

Vinyl Chloride

Vinyl chloride ($CH_2=CHCl$) is a chemical compound of increasing industrial importance. It is a monomer used as a chemical intermediate in the polymerization of polyvinyl chloride resin, in the production of copolymers such as Saran, and as a solvent.

Animal Toxicity

The toxicity of vinyl chloride has been reviewed by von Oettingen,[1] Mastromatteo, *et al.*,[2] and more recently by Torkelson, *et al.*,[3] and Lester, *et al.*[4] This gas is an anesthetic, and narcosis is the only reported effect of acute overexposure.

Torkelson,[3] Lester,[4] and their co-workers studied the chronic toxicity of vinyl chloride on rats. Torkelson and associates included rabbits, guinea pigs and dogs in a study of effects from repeated exposure, i.e., using controlled concentrations of 50-500 ppm. They found that repeated seven-hour exposure to 220 ppm caused micropathological changes in the livers of rabbits, and at 100 ppm, noted slight but statistically significant increases in the average weight of rat livers. Other animals were unaffected by 100 ppm. Using concentrations of 20,000 and 50,000 ppm, Lester found no evidence of effects on lungs or other vital organs upon repeated daily exposures lasting 92 days at the lower concentration and 19 days at the higher level. Like Torkelson, however, he detected some increase in relative weights of the rat liver and, in addition, of the rat spleen. The Committee on Threshold Limit Values (American Conference of Governmental Industrial Hygienists), weighing both studies, concluded that "although the experimental data are conflicting, the preponderance indicates a compound of relatively low toxicity with which a threshold limit of 500 ppm is consistent."[5]

Human Toxicity

Few effects have been reported as a result of human exposure to vinyl chloride except for narcosis upon acute exposure. However, at least two industrial deaths have been reported from overexposure to vinyl chloride.[6] In a controlled study, Lester, *et al.*,[4] exposed six volunteers for five-minute periods to 4,000 8,000, 12,000, 16,000, and 20,000 ppm of vinyl chloride. The first signs of intoxication appear at 8,000-12,000 ppm. No other effects were reported.

Baretta, *et al.*,[7] exposed human volunteers to 50, 250 and 500 ppm for 7 1/2 hours in an investigation concerned primarily with expired air studies. No clinical changes nor neurological responses were found in the thirteen volunteers upon thorough physical examination.

Filatova and Gronsberg[8] reported angioneurosis of spastic character in workers exposed to the monomer in a polyvinyl chloride polymerization process. Air samples usually varied between 20 ppm and 315 ppm.

Wilson, *et al.*,[9] reported several cases of acroosteolysis in hands of workmen working in vinyl chloride polymerization processes. No vinyl chloride exposure estimates are cited, but the nature of the disorder and the circumstances of its appearance suggest that the effect may have resulted from a "combination of physical insult, chemical insult, and personal idiosyncrasy." Dinman, *et al.*,[10] Cook, *et al.*,[11] and Dodson, *et al.*,[12] reported on a comprehensive epidemiological, industrial hygiene and clinical study of over 5,000 employees engaged in vinyl chloride and polyvinyl chloride manufacturing throughout the United States and Canada. A clear association of acroosteolysis and manual cleaning of polymerization reactors was revealed, with an expected prevalence of one case per 37 reactor cleaners. The study did not implicate vinyl chloride as the etiological agent but, using certain assumptions about the monomeric content of polymer residue within the reactors, there appeared to be a semi-quantitative correlation between the prevalence of acroosteolysis and the degree of degassing prior to vessel entry.[11]

Suciu, *et al.*,[13] studied the clinical manifestations of a group of 186 male employees working in polyvinyl chloride plants. They reported the presence of the "narcotic syndrome," asthenic nervous

symptoms, Raynaud's syndrome and hepatomegaly, but did not furnish data regarding the number of exposures to vinyl chloride and other substances in the work environment.

Environmental Aspects

The Work Environment

Subjects included in our investigation had worked in one or both of two manufacturing facilities which had been using vinyl chloride in polymerization processes. In both plants the environmental stresses of the work area were essentially equivalent. There were two airborne materials present in the work environment, vinyl chloride and vinylidene chloride. The concentrations of vinyl chloride were much higher than those of vinylidene chloride, due to the much larger quantities of vinyl chloride used and its greater volatility.

During the first of two decades covered in the present study, the exposure of the workers to vinyl chloride and vinylidene chloride were estimated solely by nonspecific combustion techniques.[15,16] The concentrations were expressed as vinyl chloride, although both materials were known to be present. In more recent measurements, infrared and gas chromatographic techniques have established that the vinyl chloride concentrations average 10 ppm, while virtually all vinylidene chloride concentrations amount to less than 5 ppm, and most frequently are detectable only in trace amounts. For this reason, all exposure estimates used in this study have been indexed as "vinyl chloride." Our conclusions, however, must be viewed in the proper context — that is, a work environment with two airborne materials: vinyl chloride in substantial amounts combined with very small amounts of vinylidene chloride. It should be noted, however, that a continuous 90-day inhalation exposure of rats and guinea pigs, at a concentration of 5 ppm vinylidene chloride,[14] revealed no significant changes in hematologic, biochemical, pathologic and growth-rate parameters.

Environmental Surveillance

Industrial hygiene surveys of the operations in which the workers under study were exposed started in 1950. From that time until 1959, environmental surveillance was conducted on a regular basis, but using only the traditional techniques of grab sampling and portable analyzers.[15,16] Since 1959, permanent multipoint continuous monitors have been used to estimate the exposures received by the workers studied. The application of data processing and computer technology to environmental control has allowed us to document the intensity of exposures more thoroughly and validate our continuous monitoring technique by breath sampling surveys.[7,17]

The environmental sampling related to this investigation has focused on the exposure levels of men working in eight critical job classifications. Sampling for one or more of these classifications was performed in 1950, 1951, 1952, 1953, 1954, 1955, 1958, 1959, and each year thereafter. Before continuous monitors were installed in 1959, the periodic exposure estimates were based on job studies supplemented by the examination of several discreet samples gathered over a few days. In later surveys, the exposure estimates were based on hundreds of thousands of samples gathered on a continuous basis over long time periods using multi-point analyzers. Thus the quantity of environmental sampling has increased and the quality has improved over the years in a manner that parallels the intensification of the medical surveillance program.

Suitable Air Quality Parameters

Obviously, a study of the possible effects of repeated inhalation of an airborne material which varies in concentration requires the use of a quantitative expression of air quality. We also recognize the need for an expression of air quality that will help characterize the tremendous variation in vinyl chloride concentration that may occur, together with a measure of central tendency. We base our choice, the "time-weighted average concentration" (TWA), on consideration both of the problem under study and of availability of data. For this study, from a practical viewpoint, the heterogeneity of the environmental sampling limits our choice of an air-quality parameter to the time-weighted

average concentration, which is a convenient expression for integrating a variable exposure pattern. However, we wish to point out that theoretically this expression has no relationship to the degree of toxic response.

Bartlett and Carroll [18] note that, for agents passing through the respiratory membranes, as vinyl chloride apparently does, we know very little of how repeated or continuous exposure leads to chronic effects. However, since chronic effects could presumably be cumulative and progressive, a suitable parameter for the study of air quality would be the mean concentration, *e.g.*, the time-weighted average concentration.

As a result of the environmental sampling conducted since 1950, yearly TWA estimates have been tabulated for each of the 98 individuals studied, following the work history of each man as he stayed within the group of critical job classifications during his employment. The result is a table of yearly exposure estimates for each individual. With such a table, a man's previous exposure history is available — both on a cumulative dosage basis (ppm-years) and as a career time-weighted average exposure.

Medical Aspects

Those who have worked in the industrial setting appreciate the difficulties encountered in studying a population which is subject to continuing change and often to mixed exposures. In actual experience it is rare to encounter a stable population which has had exposure to a single environmental contaminant. The population in the present study is typical in that the exposure has been mixed. Likewise, our clinical methods have varied both as to frequency of examination and use of certain laboratory tests.

Until recently, our periodic medical examination consisted of a medical history, and a physical examination, including chest x-ray, timed vital capacity, urinalysis and minimum hematology. To this basic examination we have added those particular laboratory tests which appear justified by the particular hazard to which the worker may have been exposed. The tests have varied from year to year as the state of medical knowledge has changed. We now have a program in which all employees, in addition to this basic examination, receive a far more complete battery of tests. We include all individuals in our plant, regardless of the degree or type of exposure to hazardous materials. By so doing, we hope to accumulate data that will be useful in establishing norms for our working population, and for providing better clinical data to be used in similar projects.

Data on a large group of employees that would qualify as a control group would be very useful for a conventional comparison of mean clinical indices for the "control" population and the "exposed" population. Unfortunately we have no such comparable data. Moreover, this type of analysis has the disadvantage of masking variation within the "exposed" group — variation which could be correlated with the degree of exposure if good environmental data were available.

The experience discussed in this paper is based largely on our previous methods of acquiring data. At the moment we are seeking to establish a method with which we can study the data accumulated in the past. Over the years, our examinations, which have served the basic purpose of protecting the health of individual employees, have resulted in the discovery and correction of some obvious abnormalities. However, less obvious effects may have been missed.

Though we had no ideal control group, we compared the results of the examinations on 66 of the individuals in the study group who had had examinations during 1965 and 1966 with a group of 605 employees from other departments who had had examinations in the same period. Ninety-five parameters of the history, physical examination and laboratory work were studied. This comparison was carried out by a test for difference between means, using a normal approximation. The summary of significant differences is shown in Table I. The study group showed an increased number of responses to the history item on asthma. This, however, was not reflected in a final diagnostic category, nor was any significant difference noted between the timed vital capacities of the study group and of the overall group. The study group also showed an

TABLE I

Factors in Which VCI Group Differed Significantly from the "Control Group" ($P \leq 0.05$)

	VCI Group, %	"Control Group," %
Number of Exams	66	605
History:		
Asthma	10.8	2.6
Stomach, liver, intestinal trouble	6.2	18.0
Kidney stone, bloody urine	9.2	3.0
Nervous trouble of any sort	4.6	13.4
Have you ever worked with radioactive substances	1.5	15.5
Physical:		
Anus-rectum	13.8	6.1
Identifying body marks	7.7	18.7

increase in positive responses to the history item "kidney stone or bloody urine." Again, this was not reflected in the diagnostic categories. There was a decrease in number of responses to the history questions on "stomach, liver, and intestinal trouble" and "nervous trouble of any sort." On physical examination, the only category in which more responses were recorded was that involving abnormalities of the anus and rectum. Again, since this finding was not borne out in the final diagnostic categories, it would indicate that the various examiners did not consider these findings to be of clinical significance.

There was no difference in overall diagnostic categories except for diseases of the digestive system, where fewer specific diagnoses were recorded for the study group than for the comparison group. There were no group differences in the electrocardiograms or chest x-rays. Hand x-rays on the individuals in the "exposed" group showed no significant abnormalities and no case of acroosteolysis. For comparing the mean BSP of the study group with that of the comparison group, only 116 measurements were available for the comparison group. The mean BSP for the study groups was 2.73 (50 observations), and the mean for the control group was 2.89 (116 observations). Although all records were individually reviewed for data which had not been processed statistically, no significant additional findings were noted. Considering the many factors studied, some differences would be expected. However, this conventional comparison of test means for the two groups does not suggest any basic difference between the two populations with regard to general health, and it appears that no significant disease has appeared in the study group as a result of work exposure.

Statistical Consolidation of Data for the Exposed Population

Dependent Variables

After the accumulated clinical data from the 98 men in this study had been compiled, there were 21 clinical parameters for which sufficient data existed to warrant inclusion in further statistical analysis. The criterion for inclusion was at least one observation per man for 25 men for any given test. The 21 clinical parameters are listed in Table II.

Independent Variables

In identifying factors which could explain some or all of the variation in the observed clinical variables, we recognize the need for including a record of age and obesity (important nonenvironmental variables), and the level and duration of exposure (essential environmental variables). Age was recorded to the nearest whole year. Obesity was defined as the ratio of actual weight to "standard weight." The level of exposure was expressed as the cumulative time-weighted average concentration. The product of TWA and time-on-the-job (TOJ) gave a measure of the cumulative dosage.

TABLE II

Twenty-one Clinical Parameters Screened for Correlation with Exposure

Test
Physical
Systolic blood pressure
Diastolic blood pressure
Timed vital capacity
Chemical
Bromsulphalein (BSP)
Icterus index
Alkaline phosphatase
Serum glut oxal tran (SGOT)
Thymol turbidity
Protein, serum total
albumin
globulin
alpha 1
alpha 2
beta
gamma
AG ratio
Hematological
Hemoglobin
Hematocrit
Red blood cells
White blood cells
Prothrombin time
Urine
Specific gravity

Data Format

At this point we had prepared two concurrent sets of data for each man: medical information and environmental information. All that remained was the individual matching process and collective analysis. At the time of each clinical observation, both types of data for each man were registered in the following format:

Man No., Date, Age, TOJ, TWA, Ht, Wt, Std Wt, $Y_1 \ldots Y_{21}$

Where TOJ = time-on-job (time of exposure), yrs.

TWA = Career time-weighted average exposure

Std Wt = Standard (desired) weight as tabulated by the Metropolitan Life Insurance Company.[19]

Y_i = Clinical observation i, i = 1, 2 ... 21.

Statistical Analysis

The technique used for extracting relationships hidden in the available data was "step-wise multiple linear regression analysis." This procedure, made powerful by the advent of digital computers, systematically builds a mathematical model from a choice of independent variable terms based on the fundamental independent variables. In the step-wise regression procedure, the independent variable (X_1) most highly correlated with the response is entered into the model, and the coefficients are determined by the method of least squares. Using partial correlation coefficients, the next variable (X_2) to enter the regression is that whose partial correlation with the response is highest. Given the regression equation $Y = f(X_1, X_2)$, the method now examines the contribution X_1 would have made if X_2 had been entered first. Repeatedly, the step-wise method selects as the next variable in the regression the one most highly partially correlated with the response. At each stage, the "best" regression equation $Y = f(X_1, X_2, \ldots X_n)$ is determined by the method of least squares, after checking the partial F criterion for each variable to verify the significance of each term included.[20]

The object of this technique is to express a relationship by some relatively simple mathematical function such as polynominal which contains appropriate variables and which approximates the true response of the dependent variable over some limited ranges of all the variables involved. Since this approach is empirical, the resulting equation might be considered to be physically meaningless; nevertheless, it may prove extremely valuable for predicting the values of some dependent variable from knowledge of other variables, at least under certain stated restrictions. In using the technique, it was kept in mind that, just because a particular functional relationship has been developed and a specific computational procedure is followed, it cannot be concluded that a causal relationship exists among the variables. After data had been accumulated and a strategy had been selected for analysis of the information, the remaining steps could be broadly classified as screening and refinement.

Correlation Matrix

The first step in analyzing the consolidated information was to examine the linear

TABLE III

Correlation of All Dependent Variables with All Independent Variables ($P \leq 0.05$)

Test	Age	OB	TWA	Dose
Physical				
Systolic blood pressure	+	+	+	+
Diastolic blood pressure	+	+	+	+
Timed vital capacity	–	0	0	0
Chemical				
Bromsulphalein (BSP)	0	+	+	+
Icterus index	0	0	+	+
Alkaline phosphatase	0	0	0	0
Serum glut oxal tran (SGOT)	0	0	0	0
Thymol turbidity	0	0	0	0
Protein, serum total				
albumin	0	0	0	0
globulin				
alpha 1	+	0	0	0
alpha 2	0	0	0	0
beta	0	+	+	+
gamma	–	0	0	0
AG ratio	0	0	0	0
Hematological				
Hemoglobin	–	0	–	–
Hematocrit	0	0	0	0
Red blood cells	0	0	0	0
White blood cells	0	0	0	0
Prothrombin time	0	0	0	0
Urine				
Specific gravity	0	0	0	0

correlation matrix for all the independent and dependent variables available. This screening technique revealed several clinical variables that appeared to be related to exposure. The correlation matrix is shown in Table III.

Six clinical parameters of the 21 under study showed significant correlations ($P \leq 0.05$) with the exposure variables, cumulative TWA and cumulative dose. These were: systolic and diastolic blood pressure, bromsulphalein, icterus index, hemoglobin and beta-protein. Of these, three showed correlation with age and four with obesity. Three other clinical parameters were significantly associated with age.

The correlation-screening procedure helped us develop and show that the "independent" and "dependent" variables are interrelated. Table IV shows the correlation matrix ($P \leq 0.05$) for all the crucial variables, dependent and independent. The general consistency of the relationships indicated among the variables justified more rigorous analysis.

Development of Regression Models

In the development of a linear regression equation for each clinical test Y in terms of independent variables, age, obesity, TWA, and dose, we took the view that the complete set of terms from which a model would be chosen should include the independent variables themselves, together with interaction or cross-product terms which might be helpful in explaining variation in the observed variables. For example, we allowed for the possibility of age and exposure operating together (interacting) in a manner which would be different from that of age and exposure acting independently. However, we faced two opposing criteria for selecting a predictive model:

1. For utility and accuracy we wished our model to include as many significant

TABLE IV

Correlation Coefficient Matrix – Crucial Variables

	Age	OB	TWA	Dose	BP_S	BP_D	BSP	II	Hb	β Protein
Age		0	0	+	+	+	0	0	–	0
OB	0		0	+	+	+	+	0	0	+
TWA	0	0		+	+	+	+	+	–	+
Dose	+	+	+		+	+	+	+	–	+
BP_S	+	+	+	+		+	+	0	0	0
BP_D	+	+	+	+	+		+	0	0	0
BSP	0	+	+	+	+	+		0	0	+
II	0	0	+	+	0	0	0		0	0
Hb	–	0	–	–	0	0	0	0		0
β Protein	0	+	+	+	0	0	+	0	0	

\+ Positive correlation $P \leq 0.05$
0 No correlation $P \leq 0.05$
– Negative correlation $P \leq 0.05$

TABLE V

Number of Subjects and Number of Clinical Tests within the Study Group

Test	Total Number of Observations	Number of Subjects & Number of Randomly Selected Observations
Systolic blood pressure	323	98
Diastolic blood pressure	323	98
Bromsulphalein	92	65
Icterus index	29	25
Hemoglobin	145	83
Beta-protein	58	58

independent variable terms as possible so that reliable values could be predicted.

2. For simplicity and ease of communication, we wanted the equation to include as few significant independent variable terms as possible.

Operating largely from an empirical point of view, we drew up a list of 30 independent variable terms including transformations of the four basic independent factors. Since we had unequal numbers of observations for each individual in any given test, it was necessary to choose randomly one observation per individual for each test in order to weight each man equally. This random selection reduced the number of observations for each test as indicated in Table V.

Statistical Results

The results of the regression analyses for each of the six crucial clinical variables are given below:

Systolic Blood Pressure

$BP_s = A_1 + B_1 (Age)^2 + (TWA)$
$(Age)\,[C_1 (OB) - D_1]$

Diastolic Blood Pressure

$BP_d = A_2 + B_2 (Age)^{1/2}$
$(OB)^{1/2} + C_2 (TWA)(OB)$

Bromsulphalein

$BSP = A_3 + B_3 (Age)(Dose)$

Icterus Index

$II = A_4 + B_4 (TWA)^2$

Hemoglobin

$Hb = A_5 + B_5 (Age)^{1/2} - C_5 (TWA)^2$

Beta-protein

$Beta\text{-}protein = A_6 + B_6 (Dose)^2$

Figures 1, 2 and 3 show the regression responses for three of the above models, BSP, Icterus Index and Beta-protein, respectively.

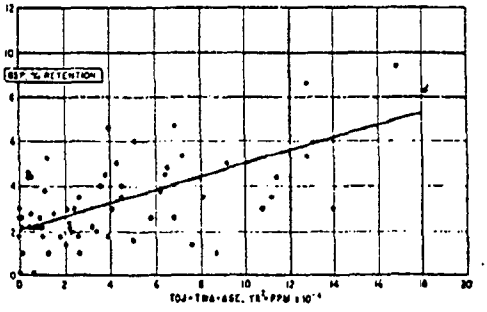

Figure 1. Regression model for bromsulphalein retention.

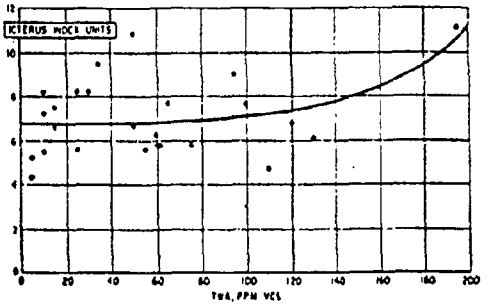

Figure 2. Regression model for icterus index.

Statistical Significance of Models

An appropriate question is: What measures of precision can be attached to the regression models? Three useful indices are the standard error of regression, Se, the overall F-Statistic, and the coefficient of multiple determination,

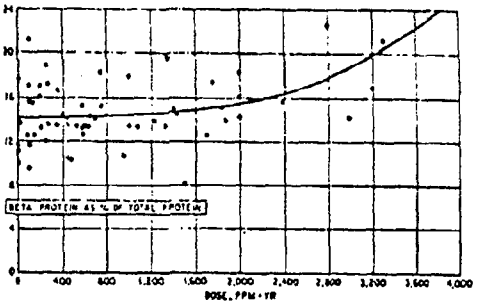

Figure 3. Regression model for beta-protein.

R^2. These measures of the "goodness of fit" for each model of the clinical variables are listed in Table VI. All of the regression models are significant at the P=0.001 level, except the Icterus Index model, which is significant at the P=0.03 level.

Utility of the Models

The regression models must be used with discretion. Since the least square regression coefficients are adjusted for other variables in the regression procedure, attempting to predict the response by changing only one variable arbitrarily may be misleading. Because of this, we must specify the prediction range for each variable under investigation. Such prediction ranges are shown in Table VII.

To relate the statistical results to the practical question of an industrial hygiene standard requires careful consideration. First, an acceptable workroom air concentration must allow for men working in the environment for an entire career, up to 45 years; our data are useful only over a 20-year span. For effects which are cumulative, as most of those isolated in this study apparently are, the last part of a man's career is the limiting consideration. In view of our data and their ranges, we can examine the clinical variables at TOJ=20, and Age=60, the highest legitimate values of our predictive parameters. In the case of blood pressure, obesity must be fixed also if we are to predict the effect of the level of exposure, TWA. For this purpose, we hold "OB" constant at 1.06, the overall mean for the blood pressure data. The following functions result:

Systolic Blood Pressure
$= 136.80 + 0.034035\ (TWA)$

Diastolic Blood Pressure
$= 84.74 + 0.018845\ (TWA)$

Bromsulphalein
$= 2.12 + 0.034599\ (TWA)$

Icterus Index
$= 6.82 + 0.000000002309522\ (TWA)^4$

Hemoglobin $= 13.97 - 0.0000000457339\ (TWA)^3$

Beta-protein $= 14.15 + 0.000001371545\ (TWA)^3$

These clinical changes are tabulated in Table VIII as a function of TWA.

Discussion of Clinical Changes

In reviewing Table VIII, we note six factors which relate empirically to exposure. Within

TABLE VI

Statistical Significance of the Regression Models

Model	Number of Observations	Standard Error of Regression	Overall F-Statistic	Coefficient of Multiple Determination
Systolic blood pressure	98	12.9	24.53 (3;94)*	0.180
Diastolic blood pressure	98	7.6	39.46 (2;95)*	0.193
Bromsulphalein	65	1.5	43.85 (1;63)*	0.407
Icterus index	25	1.6	5.66 (1;23)**	0.191
Hemoglobin	83	0.83	8.95 (2;80)*	0.162
Beta-protein	58	2.6	12.65 (1;56)*	0.170

*P < 0.001
**P = 0.03

the scope of this study the predicted blood pressures, systolic and diastolic, did not rise to levels which would be considered abnormal. The hemoglobin, though statistically decreased, does not fall outside the normal limits for our laboratory. The significance of the change in ratio of the beta-protein is not known. We are left with two factors which give some cause for concern. The changes in the Icterus Index and in the BSP lend some support to the hypothesis that some changes in liver function have occurred in a few individuals exposed at the higher levels. The BSP appears to be most significantly correlated with exposure.

Within the study group were several individuals who, after approximately 20 years of exposure with time-weighted exposures of approximately 300 ppm of vinyl chloride and smaller amounts of vinylidene chloride during the early part of their careers, demonstrated a tendency to develop changes in certain laboratory tests which appear to be related to their exposure. Reference to Figures 1-3 indicates that our interpretation of the clinical changes must be tempered by the fact that only a small number of individuals experienced the highest exposures.

Two of the individuals showing the highest rise in BSP were rechecked in 1968. One had essentially normal laboratory findings and the other showed persistent elevation of various liver function tests, even though both had been removed from further exposure since 1965. The individual whose liver function tests remained elevated had a history of hepatitis preceding his exposure, although his pre-exposure liver function tests had been normal. Whether his abnormalities represented a result of his exposure or independent sequelae of hepatitis cannot be ascertained. Certainly it would be desirable not to consider individuals with a history of hepatitis as candidates for prolonged exposure to vinyl or vinylidene chloride. Unfortunately, since many cases of subclinical hepatitis occur, there may always be some individuals in a working population who have had hepatitis.

For most individuals in the study, the highest exposure occurred in the early phases of their careers and their later exposures were much lower. In the final analysis, much weight had

TABLE VII

Means, Standard Deviations and Limits for Clinical Tests

	Mean	SD	Limit	Age Mean	Age SD	Age Limit	TOJ Mean	TOJ SD	TOJ Limit	TWA Mean	TWA SD	TWA Limit
Systolic blood pressure	128	14	188	40	10	65	10	5.0	25	80	75	375
Diastolic blood pressure	81	8	109	40	10	65	10	5.0	25	80	75	375
Bromsulphalein	3.3	1.9	9.4	41	11	65	11	5.3	25	75	70	340
Icterus index	7.0	1.8	11.1	40	7.1	52	14	5.7	25	55	45	200
Hemoglobin	14.5	0.9	16.4	40	10	64	9.4	4.8	20	70	70	315
Beta-protein	14.7	2.9	22.6	42	10	65	12	5.0	23	60	50	300

TABLE VIII

Expected Response of Clinical Tests as a Function of Career TWA

Test	TWA, PPM Vinyl Chloride						
	0	50	100	150	200	250	300
Systolic blood pressure (Age = 60, OBES = 1.06)	136.8	138.5	140.2	141.9	143.6	145.3	147.0
Diastolic blood pressure (Age = 60, OBES = 1.06)	84.7	85.7	86.6	87.6	88.5	89.4	90.4
Bromsulphalein (TOJ = 20, Age = 60)	2.1	3.8	5.6	7.3	9.0	10.8	12.5
Icterus index	6.8	6.8	7.0	8.1	11.0	X	X
Hemoglobin	14.0	14.0	13.9	13.8	13.6	13.3	12.7
Beta-protein	14.1	14.3	15.5	18.8	25.1	X	X

X = beyond range of available data

to be placed on the readings observed for those employees who experienced high exposure levels, especially during the period 1950-58. For example, the average time-weighted exposure level in 1950 was 155 ppm, whereas the average exposure level in 1965 was 30 ppm.

Our findings suggest that repeated exposure to vinyl chloride at TWA levels of 300 ppm or above for a working lifetime together with a very low level of vinylidene chloride may result in slight changes in certain physiologic and clinical laboratory parameters. The possibility of some impairment in liver function tests must be considered, even though no overt clinical disease was evident in any of the individuals studied. We shall continue our study, but suggest that similar studies to help clarify the effects of this material be performed for other worker populations exposed to vinyl chloride alone.

Conclusions

The present study offers a technique of judging exposure effects on a group of exposed workmen based on an analysis which is intended to account for individual levels of exposure rather than relying on a collective comparison with a so-called "control" population. The "exposed" group, especially when it is drawn from an industrial setting, will contain individuals subject to a wide range of exposures, and the mean clinical indices for the group may well mask significant individual differences within the exposed group that could be detected only by intra-group analysis.

We have attempted to correlate the clinical manifestations of a group of men for which exposure data as well as clinical measurements were available. With this approach, the "exposed" group will contain some individuals whose exposures are low enough to serve as "controls." The regression technique we have employed treats the exposure levels (Dose and TWA) as independent variables, thereby providing an open format that allows inclusion of any degree of exposure, including none. The advantage of regression analysis in this application lies in the ability to extract more substantial information on acceptable exposure levels by relating measured clinical changes directly to measured exposure. To use this method, good environmental and medical data must be gathered and consolidated concurrently in substantial quantity.

We have demonstrated the use of this statistical technique with a group of men exposed to vinyl chloride and trace levels of vinylidene chloride. In so doing, we have found some interesting apparent effects from chronic exposure to that system but, more importantly, the methodology looks promising as a needed improvement in our quest to make

practical use of toxicological feedback from worker exposures. We hope that others will offer further refinements and suggestions that will help attain this goal.

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CASE REPORTS

Hepatic Angiosarcoma

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A patient with hepatic angiosarcoma is described. The significant aspects of this malignancy are delineated. This tumor constitutes only 2% of all primary tumors of the liver. The association with exposure to vinyl chloride and other carcinogens is reviewed. Diagnostic and therapeutic modalities are discussed.

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Angiosarcoma of the liver is a rare tumor with a rapidly fatal course. A review of the English literature reveals only 103 such cases. This report describes a case of hepatic angiosarcoma notable for its brief duration of antecedent symptoms and presents a review of the etiologic, diagnostic, and therapeutic features.

CASE REPORT

A 43-year-old man with a past medical history of non-insulin-dependent diabetes mellitus, nephrolithiasis, cholecystectomy, and appendectomy presented to St. Vincent's Medical Center, Bridgeport, Connecticut, with right-sided flank and abdominal pain of 1 day's duration. He described the pain as sharp, persistent, nonradiating, and not associated with position or meals. He had experienced similar pain 1 month previously, which had resolved without treatment. He denied weight loss, anorexia, melena, vomiting, or a change in bowel habits. Glipizide was the only medication he was taking at the time. A Navy veteran and later a machinist in a brake manufacturing company, he denied knowledge of exposure to chemical toxins.

Physical examination was significant for a soft abdomen with a well-healed midline surgical scar, tenderness to palpation in the right upper quadrant, normoactive bowel sounds, and no abdominal bruits. His liver was palpable 5 cm below the right costal margin and was firm and had a smooth surface. Splenomegaly was not present. Costovertebral angle tenderness was elicited on the right side. The remainder of the physical examination was normal.

The initial laboratory tests revealed a hemoglobin of 15.4 g/dL (normal: 14 to 18); glucose of 325 mg/dL (normal: 70 to 108); lipase 206 IU/dL (normal: 23 to 208); serum glutamic oxaloacetic transaminase 27 IU/dL (normal: 12 to 45); serum glutamic pyruvic transminase 36 IU/dL (normal: 7 to 40); total bilirubin 6.4 g/dL (normal: 6.1 to 8); and alkaline phosphatase 70 IU/L (normal: 37 to 107 IU/L). Urine analysis showed 0.5% glucose, traces of blood, and no protein.

Radiologic evaluation included abdominal radiographs that were normal. An abdominal ultrasound revealed a 10-cm round mass in the right lobe of the liver, with a well-defined margin and a homoge-

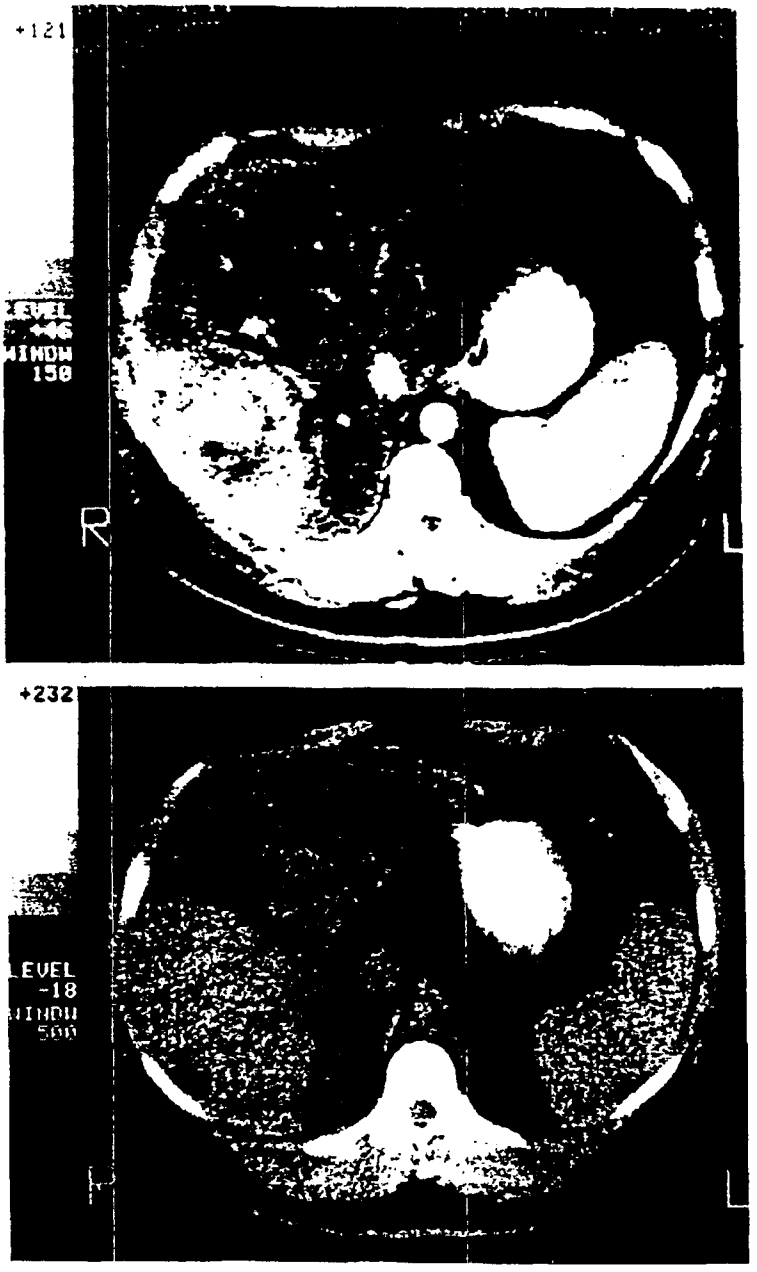

Figure 1. Top, computed tomographic scan of a hepatic angiosarcoma with contrast showing inhomogenous contrast enhancement of mass lesion, which is indicative of its vascular nature. **Bottom,** computed tomographic scan without contrast showing a predominantly homogenous 10-cm mass lesion in the right lobe of the liver that is of greater density than the remaining liver parenchyma.

neous pattern of echogenicity. A computed tomographic (CT) scan of the abdomen with and without contrast (**Figure 1**) confirmed its presence. The predominantly homogeneous mass lesion showed inhomogeneous contrast enhancement, indicating its vascular nature. The remainder of the liver appeared fatty.

Subsequently, a CT-guided needle aspirate biopsy was performed that demonstrated a pleomorphic malignant cellular process with vascular channels and scant to abundant cytoplasm. No normal tissue was present (**Figure 2**). A diagnosis of hepatic angiosarcoma was made on the basis of hematoxylin and eosin, factor VIII, and immunoperoxidase histologic studies.

To further assess this mass, hepatic arteriography was performed. This showed a large neoplastic lesion in the right lobe of the liver, with accumula-

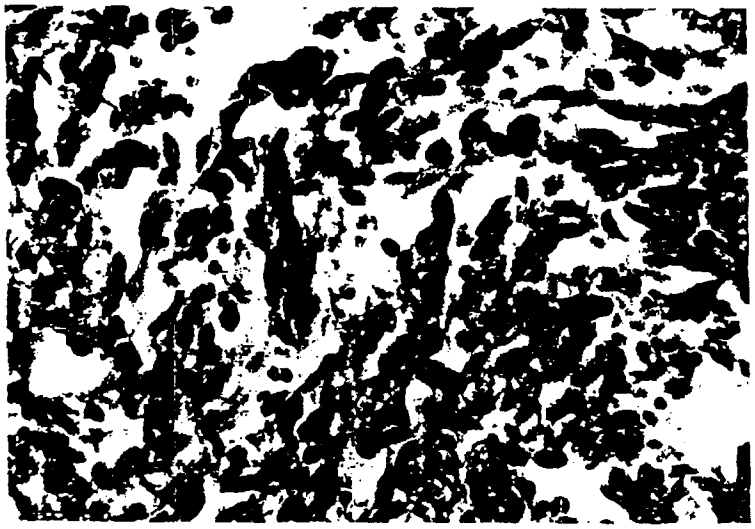

Figure 2. Angiosarcoma. Histologic pleomorphic cellular malignant process with the suggestion of vascular channels and hyaline pink to lavender, scant to abundant cytoplasm (hematoxylin and eosin stain; original magnification ×400, reduced by 30%).

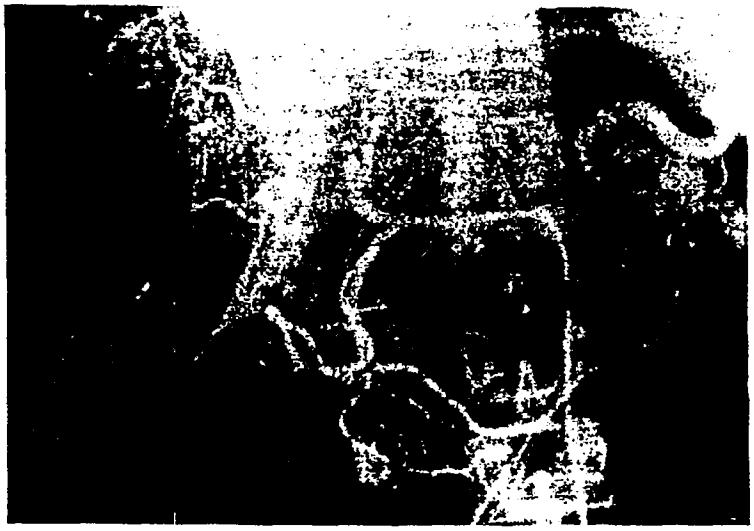

Figure 3. Hepatic angiogram showing a large 10-cm vascular mass in the right lobe of the liver with displacement of the normal vasculature and the presence of multiple vascular lakes. The left lobe is not involved.

tion of contrast in small "lakes" (**Figure 3**). There was no evidence of left-sided or portal vein involvement.

The patient was referred to Yale-New Haven Hospital for surgical consultation. Based on the assessment that the disease was limited to one lobe and that the remainder of the liver was essentially normal, a right lobectomy was performed.

COMMENTS

Angiosarcoma of the liver, which is also known as hemangioendothelial sarcoma, constitutes only 2% of all primary tumors of the liver [1]. Metastatic cancer is the most common neoplasm of the liver and is responsible for 38% of all tumors in the liver. Worldwide, hepatocellular carcinoma accounts for less than 2% of all malignancies and is responsible for 1,250,000 deaths per year in the United States. About 90% of primary carcinomas of the liver are hepatocellular carcinoma and 7% are cholangiocarcinomas; less common tumors include hepatoblastoma, angiosarcoma, and sarcoma [2].

Angiosarcoma of the liver has demonstrated the intimate relationship that exists between environment and malignant transformation. This neoplasm was first reported in association with exposure to thorotrast [3] and arsenic [4], and later with vinyl chloride by Creech and Johnson in 1974 [5]. Their studies demonstrated an increased risk of liver angiosarcoma and cancer of other sites among

employees of vinyl chloride polymerization facilities. The risk approaches 10 to 15 times that of the general population (for angiosarcoma of the liver) [6]. This rare neoplasm has also been associated with systemic diseases, i.e., hemochromatosis [7] and von Recklinghausen's disease [8]. It is also noted to be four times more prevalent in middle-aged men than middle-aged women [2].

Clinically, patients with hepatic angiosarcoma generally present with nonspecific symptoms. Prominent among the symptoms noted in a study of 103 patients were abdominal pain (the most prevalent), weakness, fatigue, and weight loss. Hepatomegaly, ascites, and jaundice were the three most common presenting signs [1]. Additionally, audible hepatic bruits on auscultation reflect the arteriovenous shunting created by these highly vascular tumors.

Hepatic arteriography provides the best tool for diagnosing vascular lesions [9]. Typically, there is movement of contrast into small "vascular lakes," central areas of hypovascularity, and peripheral contrast staining. The hepatic artery may often be displaced by the tumor. This may be observed on angiography [10]. Locker *et al* [1], in their review of patients with hepatic angiosarcoma, found that laboratory data occasionally suggested liver disease but were often nonspecific indicators.

Microscopic examination reveals malignant cells invading liver parenchyma and vasoformative areas, with vessels lined by malignant endothelial cells. The sinusoids are lined by enlarged anaplastic tumor cells, with nuclear hyperchromatism and a high nuclear-to-cytoplasmic ratio [1]. The histologic changes seen after exposure to vinyl chloride usually begin with focal hyperplasia in both hepatocytes and sinusoidal cells. These lesions are usually irregularly sized cavities within the liver parenchyma. The irregular and often striking sinusoidal dilatation is a frequently associated finding. The malignant transformation is believed to originate from this lesion.

The prognosis of patients with hepatic angiosarcoma is poor. There is often a rapid decline in the patient's condition after diagnosis, with a median survival of only 6 months. It is essentially an incurable disease that is often unresectable at the time of diagnosis. However, in a small series of patients, intravenous doxorubicin, given for 3 to 4 weeks in combination with cyclophosphamide, has had some benefit in causing temporary regression of the tumor size. This regimen of chemotherapy has improved median survival to 13 months [6]. Hepatic angiosarcoma is relatively radioresistant. Radiotherapy was attempted in one patient whose tumor was limited to one lobe and who was not considered a candidate for surgical resection. However, subsequent histologic examination at the time of autopsy showed no viable hepatocytes, although there were tumor cells in the irradiated lobe [11].

Angiosarcoma of the liver may also be surgically resected. Bonneton *et al* [13] reported on the successful removal of a tumor by right hepatic lobectomy in a worker exposed to vinyl chloride. However, the patient died weeks later of bleeding varices. No tumor was found in the liver or elsewhere at autopsy [5]. Surgery may be an option when the angiogram has revealed that the tumor is localized to one lobe and the remainder of the liver is not compromised [12].

Further therapeutic approaches using neoadjuvant chemotherapy via a hepatic artery catheter may prove useful in permitting resection in more cases. This option needs more research, although the relative scarcity of this neoplasm will add to the difficulty in evaluating this approach.

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The Correlation of Clinical and Environmental Measurements for Workers Exposed to Vinyl Chloride

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A method is described for the statistical consolidation and correlation of environmental measurements and clinical findings using as an example a group of healthy male workers exposed routinely to vinyl chloride for periods up to 25 years. Retrospective in nature the study reveals several statistically significant effects from chronic exposures to vinyl chloride and traces of vinylidene chloride.

Introduction

For validating an industrial hygiene standard, it is essential to perform careful and comprehensive studies of the possible effects of substances on exposed workmen. In practice, however, very few substances have been the object of sufficient study to furnish reliable guidelines. Today, specialists in occupational health must recognize the need to develop programs which will better identify the relation between stresses acting on the human body in the work environment and physical changes that can be measured clinically, to explain the significance of these changes and use the results to help refine our guidelines for environmental control.

Although toxicologists are constantly predicting what exposures are likely to be safe for people, there will always be some doubt about their predictions until enough human experience has been gained to prove their accuracy. The "proof of the pudding" should result from the correlation of good environmental measurements with the results of a well planned medical surveillance program. It is likely that such feedback from human experience will differ from the animal experimental data in that it will not define a level of exposure which will actually cause injury, at least frank injury. However, except in cases where an industrial hygiene standard has not been applied, the feedback from human experience could be expected to describe levels of exposure which have been shown to be either acceptable or marginally unacceptable. This information would be valuable to toxicologists because it would strengthen their skills in predicting from experimental animal data effects of substances on humans. In a broader sense, it would be useful in substantiating criteria to be used for industrial hygiene standards.

For several years The Dow Chemical Company's medical and environmental health groups have been conducting concurrent medical and environmental surveillance of a large worker population exposed to many different chemicals. The project described in this paper analyzes the information already gained from concurrent surveillance and relates it to the determination of acceptable levels of exposure. A method is described for the statistical consolidation and correlation of environmental measurements and clinical findings, using as an example a group of 98 healthy male workers who had been exposed routinely to vinyl chloride for periods up to 25 years. Retrospective in nature, the study reveals several statistically significant clinical changes due to chronic exposures to vinyl chloride and smaller amounts of vinylidene chloride. By isolating these apparent effects and examining them in the light of our medical interpretation, we have developed what appears to be a promising technique for

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relating clinical information to worker exposures to achieve a more refined industrial hygiene standard.

Vinyl Chloride

Vinyl chloride ($CH_2=CHCl$) is a chemical compound of increasing industrial importance. It is a monomer used as a chemical intermediate in the polymerization of polyvinyl chloride resin, in the production of copolymers such as Saran, and as a solvent.

Animal Toxicity

The toxicity of vinyl chloride has been reviewed by von Oettingen,[1] Mastromatteo, *et al.*,[2] and more recently by Torkelson, *et al.*,[3] and Lester, *et al.*[4] This gas is an anesthetic, and narcosis is the only reported effect of acute overexposure.

Torkelson,[3] Lester,[4] and their co-workers studied the chronic toxicity of vinyl chloride on rats. Torkelson and associates included rabbits, guinea pigs and dogs in a study of effects from repeated exposure, i.e., using controlled concentrations of 50-500 ppm. They found that repeated seven-hour exposure to 220 ppm caused micropathological changes in the livers of rabbits, and at 100 ppm, noted slight but statistically significant increases in the average weight of rat livers. Other animals were unaffected by 100 ppm. Using concentrations of 20,000 and 50,000 ppm, Lester found no evidence of effects on lungs or other vital organs upon repeated daily exposures lasting 92 days at the lower concentration and 19 days at the higher level. Like Torkelson, however, he detected some increase in relative weights of the rat liver and, in addition, of the rat spleen. The Committee on Threshold Limit Values (American Conference of Governmental Industrial Hygienists), weighing both studies, concluded that "although the experimental data are conflicting, the preponderance indicates a compound of relatively low toxicity with which a threshold limit of 500 ppm is consistent."[5]

Human Toxicity

Few effects have been reported as a result of human exposure to vinyl chloride except for narcosis upon acute exposure. However, at least two industrial deaths have been reported from overexposure to vinyl chloride.[6] In a controlled study, Lester, *et al.*,[4] exposed six volunteers for five-minute periods to 4,000, 8,000, 12,000, 16,000, and 20,000 ppm of vinyl chloride. The first signs of intoxication appear at 8,000-12,000 ppm. No other effects were reported.

Baretta, *et al.*,[7] exposed human volunteers to 50, 250 and 500 ppm for 7 1/2 hours in an investigation concerned primarily with expired air studies. No clinical changes nor neurological responses were found in the thirteen volunteers upon thorough physical examination.

Filatova and Gronsberg[8] reported angioneurosis of spastic character in workers exposed to the monomer in a polyvinyl chloride polymerization process. Air samples usually varied between 20 ppm and 315 ppm.

Wilson, *et al.*,[9] reported several cases of acroosteolysis in hands of workmen working in vinyl chloride polymerization processes. No vinyl chloride exposure estimates are cited, but the nature of the disorder and the circumstances of its appearance suggest that the effect may have resulted from a "combination of physical insult, chemical insult, and personal idiosyncrasy." Dinman, *et al.*,[10] Cook, *et al.*,[11] and Dodson, *et al.*,[12] reported on a comprehensive epidemiological, industrial hygiene and clinical study of over 5,000 employees engaged in vinyl chloride and polyvinyl chloride manufacturing throughout the United States and Canada. A clear association of acroosteolysis and manual cleaning of polymerization reactors was revealed, with an expected prevalence of one case per 37 reactor cleaners. The study did not implicate vinyl chloride as the etiological agent but, using certain assumptions about the monomeric content of polymer residue within the reactors, there appeared to be a semi-quantitative correlation between the prevalence of acroosteolysis and the degree of degassing prior to vessel entry.[11]

Suciu, *et al.*,[13] studied the clinical manifestations of a group of 186 male employees working in polyvinyl chloride plants. They reported the presence of the "narcotic syndrome," asthenic nervous

symptoms, Raynaud's syndrome and hepatomegaly, but did not furnish data regarding the number of exposures to vinyl chloride and other substances in the work environment.

Environmental Aspects

The Work Environment

Subjects included in our investigation had worked in one or both of two manufacturing facilities which had been using vinyl chloride in polymerization processes. In both plants the environmental stresses of the work area were essentially equivalent. There were two airborne materials present in the work environment, vinyl chloride and vinylidene chloride. The concentrations of vinyl chloride were much higher than those of vinylidene chloride, due to the much larger quantities of vinyl chloride used and its greater volatility.

During the first of two decades covered in the present study, the exposure of the workers to vinyl chloride and vinylidene chloride were generated solely by nonspecific combustion techniques.[15,16] The concentrations were expressed as vinyl chloride, although both materials were known to be present. In more recent measurements, infrared and gas chromatographic techniques have established that the vinyl chloride concentrations average 10 ppm, while virtually all vinylidene chloride concentrations amount to less than 5 ppm, and most frequently are detectable only in trace amounts. For this reason, all exposure estimates used in this study have been indexed as "vinyl chloride." Our conclusions, however, must be viewed in the proper context — that is, a work environment with two airborne materials: vinyl chloride in substantial amounts combined with very small amounts of vinylidene chloride. It should be noted, however, that a continuous 90-day inhalation exposure of rats and guinea pigs, at a concentration of 5 ppm vinylidene chloride,[14] revealed no significant changes in hematologic, biochemical, pathologic and growth-rate parameters.

Environmental Surveillance

Industrial hygiene surveys of the operations in which the workers under study were exposed started in 1950. From that time until 1959, environmental surveillance was conducted on a regular basis, but using only the traditional techniques of grab sampling and portable analyzers.[15,16] Since 1959, permanent multipoint continuous monitors have been used to estimate the exposures received by the workers studied. The application of data processing and computer technology to environmental control has allowed us to document the intensity of exposures more thoroughly and validate our continuous monitoring technique by breath sampling surveys.[7,17]

The environmental sampling related to this investigation has focused on the exposure levels of men working in eight critical job classifications. Sampling for one or more of these classifications was performed in 1950, 1951, 1952, 1953, 1954, 1955, 1958, 1959, and each year thereafter. Before continuous monitors were installed in 1959, the periodic exposure estimates were based on job studies supplemented by the examination of several discreet samples gathered over a few days. In later surveys, the exposure estimates were based on hundreds of thousands of samples gathered on a continuous basis over long time periods using multi-point analyzers. Thus the quantity of environmental sampling has increased and the quality has improved over the years in a manner that parallels the intensification of the medical surveillance program.

Suitable Air Quality Parameters

Obviously, a study of the possible effects of repeated inhalation of an airborne material which varies in concentration requires the use of a quantitative expression of air quality. We also recognize the need for an expression of air quality that will help characterize the tremendous variation in vinyl chloride concentration that may occur, together with a measure of central tendency. We base our choice, the "time-weighted average concentration" (TWA), on consideration both of the problem under study and of availability of data. For this study, from a practical viewpoint, the heterogeneity of the environmental sampling limits our choice of an air-quality parameter to the time-weighted

average concentration, which is a convenient expression for integrating a variable exposure pattern. However, we wish to point out that theoretically this expression has no relationship to the degree of toxic response.

Bartlett and Carroll [18] note that, for agents passing through the respiratory membranes, as vinyl chloride apparently does, we know very little of how repeated or continuous exposure leads to chronic effects. However, since chronic effects could presumably be cumulative and progressive, a suitable parameter for the study of air quality would be the mean concentration, *e.g.*, the time-weighted average concentration.

As a result of the environmental sampling conducted since 1950, yearly TWA estimates have been tabulated for each of the 98 individuals studied, following the work history of each man as he stayed within the group of critical job classifications during his employment. The result is a table of yearly exposure estimates for each individual. With such a table, a man's previous exposure history is available — both on a cumulative dosage basis (ppm-years) and as a career time-weighted average exposure.

Medical Aspects

Those who have worked in the industrial setting appreciate the difficulties encountered in studying a population which is subject to continuing change and often to mixed exposures. In actual experience it is rare to encounter a stable population which has had exposure to a single environmental contaminant. The population in the present study is typical in that the exposure has been mixed. Likewise, our clinical methods have varied both as to frequency of examination and use of certain laboratory tests.

Until recently, our periodic medical examination consisted of a medical history, and a physical examination, including chest x-ray, timed vital capacity, urinalysis and minimum hematology. To this basic examination we have added those particular laboratory tests which appear justified by the particular hazard to which the worker may have been exposed. The tests have varied from year to year as the state of medical knowledge has changed. We now have a program in which all employees, in addition to this basic examination, receive a far more complete battery of tests. We include all individuals in our plant, regardless of the degree or type of exposure to hazardous materials. By so doing, we hope to accumulate data that will be useful in establishing norms for our working population, and for providing better clinical data to be used in similar projects.

Data on a large group of employees that would qualify as a control group would be very useful for a conventional comparison of mean clinical indices for the "control" population and the "exposed" population. Unfortunately we have no such comparable data. Moreover, this type of analysis has the disadvantage of masking variation within the "exposed" group — variation which could be correlated with the degree of exposure if good environmental data were available.

The experience discussed in this paper is based largely on our previous methods of acquiring data. At the moment we are seeking to establish a method with which we can study the data accumulated in the past. Over the years, our examinations, which have served the basic purpose of protecting the health of individual employees, have resulted in the discovery and correction of some obvious abnormalities. However, less obvious effects may have been missed.

Though we had no ideal control group, we compared the results of the examinations on 66 of the individuals in the study group who had had examinations during 1965 and 1966 with a group of 605 employees from other departments who had had examinations in the same period. Ninety-five parameters of the history, physical examination and laboratory work were studied. This comparison was carried out by a test for difference between means, using a normal approximation. The summary of significant differences is shown in Table I. The study group showed an increased number of responses to the history item on asthma. This, however, was not reflected in a final diagnostic category, nor was any significant difference noted between the timed vital capacities of the study group and of the overall group. The study group also showed an

TABLE I

Factors in Which VC1 Group Differed Significantly from the "Control Group" ($P \leq 0.05$)

	VC1 Group, %	"Control Group," %
Number of Exams	66	605
History:		
Asthma	10.8	2.6
Stomach, liver, intestinal trouble	6.2	18.0
Kidney stone, bloody urine	9.2	3.0
Nervous trouble of any sort	4.6	13.4
Have you ever worked with radioactive substances	1.5	15.5
Physical:		
Anus-rectum	13.8	6.1
Identifying body marks	7.7	18.7

increase in positive responses to the history item "kidney stone or bloody urine." Again, this was not reflected in the diagnostic categories. There was a decrease in number of responses to the history questions on "stomach, liver, and intestinal trouble" and "nervous trouble of any sort." On physical examination, the only category in which more responses were recorded was that involving abnormalities of the anus and rectum. Again, since this finding was not borne out in the final diagnostic categories, it would indicate that the various examiners did not consider these findings to be of clinical significance.

There was no difference in overall diagnostic categories except for diseases of the digestive system, where fewer specific diagnoses were recorded for the study group than for the comparison group. There were no group differences in the electrocardiograms or chest x-rays. Hand x-rays on the individuals in the "exposed" group showed no significant abnormalities and no case of acroosteolysis. For comparing the mean BSP of the study group with that of the comparison group, only 116 measurements were available for the comparison group. The mean BSP for the study groups was 2.73 (50 observations), and the mean for the control group was 2.89 (116 observations). Although all records were individually reviewed for data which had not been processed statistically, no significant additional findings were noted. Considering the many factors studied, some differences would be expected. However, this conventional comparison of test means for the two groups does not suggest any basic difference between the two populations with regard to general health, and it appears that no significant disease has appeared in the study group as a result of work exposure.

Statistical Consolidation of Data for the Exposed Population

Dependent Variables

After the accumulated clinical data from the 98 men in this study had been compiled, there were 21 clinical parameters for which sufficient data existed to warrant inclusion in further statistical analysis. The criterion for inclusion was at least one observation per man for 25 men for any given test. The 21 clinical parameters are listed in Table II.

Independent Variables

In identifying factors which could explain some or all of the variation in the observed clinical variables, we recognize the need for including a record of age and obesity (important nonenvironmental variables), and the level and duration of exposure (essential environmental variables). Age was recorded to the nearest whole year. Obesity was defined as the ratio of actual weight to "standard weight." The level of exposure was expressed as the cumulative time-weighted average concentration. The product of TWA and time-on-the-job (TOJ) gave a measure of the cumulative dosage.

TABLE II

Twenty-one Clinical Parameters Screened for Correlation with Exposure

Test
Physical
Systolic blood pressure
Diastolic blood pressure
Timed vital capacity
Chemical
Bromsulphalein (BSP)
Icterus index
Alkaline phosphatase
Serum glut oxal tran (SGOT)
Thymol turbidity
Protein, serum total
albumin
globulin
alpha 1
alpha 2
beta
gamma
AG ratio
Hematological
Hemoglobin
Hematocrit
Red blood cells
White blood cells
Prothrombin time
Urine
Specific gravity

Data Format

At this point we had prepared two concurrent sets of data for each man: medical information and environmental information. All that remained was the individual matching process and collective analysis. At the time of each clinical observation, both types of data for each man were registered in the following format:

Man No., Date, Age, TOJ, TWA, Ht, Wt, Std Wt, $Y_1 \ldots Y_{21}$

Where TOJ = time-on-job (time of exposure), yrs.

TWA = Career time-weighted average exposure

Std Wt = Standard (desired) weight as tabulated by the Metropolitan Life Insurance Company.[19]

Y_i = Clinical observation i, i = 1, 2 ... 21.

Statistical Analysis

The technique used for extracting relationships hidden in the available data was "step-wise multiple linear regression analysis." This procedure, made powerful by the advent of digital computers, systematically builds a mathematical model from a choice of independent variable terms based on the fundamental independent variables. In the step-wise regression procedure, the independent variable (X_1) most highly correlated with the response is entered into the model, and the coefficients are determined by the method of least squares. Using partial correlation coefficients, the next variable (X_2) to enter the regression is that whose partial correlation with the response is highest. Given the regression equation $Y = f(X_1, X_2)$, the method now examines the contribution X_1 would have made if X_2 had been entered first. Repeatedly, the step-wise method selects as the next variable in the regression the one most highly partially correlated with the response. At each stage, the "best" regression equation $Y = f(X_1, X_2, \ldots X_n)$ is determined by the method of least squares, after checking the partial F criterion for each variable to verify the significance of each term included.[20]

The object of this technique is to express a relationship by some relatively simple mathematical function such as polynominal which contains appropriate variables and which approximates the true response of the dependent variable over some limited ranges of all the variables involved. Since this approach is empirical, the resulting equation might be considered to be physically meaningless; nevertheless, it may prove extremely valuable for predicting the values of some dependent variable from knowledge of other variables, at least under certain stated restrictions. In using the technique, it was kept in mind that, just because a particular functional relationship has been developed and a specific computational procedure is followed, it cannot be concluded that a causal relationship exists among the variables. After data had been accumulated and a strategy had been selected for analysis of the information, the remaining steps could be broadly classified as screening and refinement.

Correlation Matrix

The first step in analyzing the consolidated information was to examine the linear

TABLE III

Correlation of All Dependent Variables with All Independent Variables ($P \leq 0.05$)

Test	Age	OB	TWA	Dose
Physical				
Systolic blood pressure	+	+	+	+
Diastolic blood pressure	+	+	+	+
Timed vital capacity	–	0	0	0
Chemical				
Bromsulphalein (BSP)	0	+	+	+
Icterus index	0	0	+	+
Alkaline phosphatase	0	0	0	0
Serum glut oxal tran (SGOT)	0	0	0	0
Thymol turbidity	0	0	0	0
Protein, serum total				
albumin	0	0	0	0
globulin				
alpha 1	+	0	0	0
alpha 2	0	0	0	0
beta	0	+	+	+
gamma	–	0	0	0
A/G ratio	0	0	0	0
Hematological				
Hemoglobin	–	0	–	–
Hematocrit	0	0	0	0
Red blood cells	0	0	0	0
White blood cells	0	0	0	0
Prothrombin time	0	0	0	0
Urine				
Specific gravity	0	0	0	0

correlation matrix for all the independent and dependent variables available. This screening technique revealed several clinical variables that appeared to be related to exposure. The correlation matrix is shown in Table III.

Six clinical parameters of the 21 under study showed significant correlations ($P \leq 0.05$) with the exposure variables, cumulative TWA and cumulative dose. These were: systolic and diastolic blood pressure, bromsulphalein, icterus index, hemoglobin and beta-protein. Of these, three showed correlation with age and four with obesity. Three other clinical parameters were significantly associated with age.

The correlation-screening procedure helped us develop and show that the "independent" and "dependent" variables are interrelated. Table IV shows the correlation matrix ($P \leq 0.05$) for all the crucial variables, dependent and independent. The general consistency of the relationships indicated among the variables justified more rigorous analysis.

Development of Regression Models

In the development of a linear regression equation for each clinical test Y in terms of independent variables, age, obesity, TWA, and dose, we took the view that the complete set of terms from which a model would be chosen should include the independent variables themselves, together with interaction or cross-product terms which might be helpful in explaining variation in the observed variables. For example, we allowed for the possibility of age and exposure operating together (interacting) in a manner which would be different from that of age and exposure acting independently. However, we faced two opposing criteria for selecting a predictive model:

1. For utility and accuracy we wished our model to include as many significant

TABLE IV

Correlation Coefficient Matrix – Crucial Variables

	Age	OB	TWA	Dose	BP_S	BP_D	BSP	II	Hb	β Protein
Age		0	0	+	+	+	0	0	–	0
OB	0		0	+	+	+	+	0	0	+
TWA	0	0		+	+	+	+	+	–	+
Dose	+	+	+		+	+	+	+	–	+
BP_S	+	+	+	+		+	+	0	0	0
BP_D	+	+	+	+	+		+	0	0	0
BSP	0	+	+	+	+	+		0	0	+
II	0	0	+	+	0	0	0		0	0
Hb	–	0	–	–	0	0	0	0		0
β Protein	0	+	+	+	0	0	+	0	0	

+ Positive correlation $P \leq 0.05$
0 No correlation $P \leq 0.05$
– Negative correlation $P \leq 0.05$

TABLE V

Number of Subjects and Number of Clinical Tests within the Study Group

Test	Total Number of Observations	Number of Subjects & Number of Randomly Selected Observations
Systolic blood pressure	323	98
Diastolic blood pressure	323	98
Bromsulphalein	92	65
Icterus index	29	25
Hemoglobin	145	83
Beta-protein	58	58

independent variable terms as possible so that reliable values could be predicted.

2. For simplicity and ease of communication, we wanted the equation to include as few significant independent variable terms as possible.

Operating largely from an empirical point of view, we drew up a list of 30 independent variable terms including transformations of the four basic independent factors. Since we had unequal numbers of observations for each individual in any given test, it was necessary to choose randomly one observation per individual for each test in order to weight each man equally. This random selection reduced the number of observations for each test as indicated in Table V.

Statistical Results

The results of the regression analyses for each of the six crucial clinical variables are given below:

Systolic Blood Pressure

$BP_s = A_1 + B_1 (Age)^{\frac{1}{2}} + (TWA)$
$(Age)\,[C_1 (OB) - D_1]$

Diastolic Blood Pressure

$BP_d = A_2 + B_2 (Age)^{\frac{1}{2}}$
$(OB)^{\frac{1}{2}} + C_2 (TWA)(OB)$

Bromsulphalein

$BSP = A_3 + B_3 (Age)(Dose)$

Icterus Index

$II = A_4 + B_4 (TWA)^4$

Hemoglobin

$Hb = A_5 + B_5 (Age)^{\frac{1}{2}} - C_5 (TWA)^3$

Beta-protein

$Beta\text{-}protein = A_6 + B_6 (Dose)^3$

Figures 1, 2 and 3 show the regression responses for three of the above models, BSP, Icterus Index and Beta-protein, respectively.

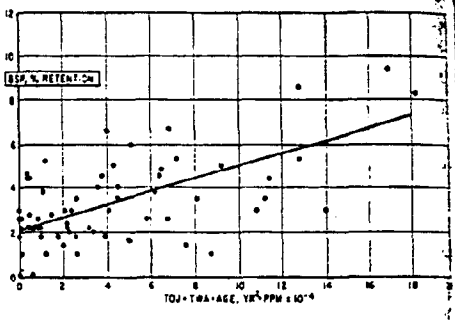

Figure 1. Regression model for bromsulphalein retention.

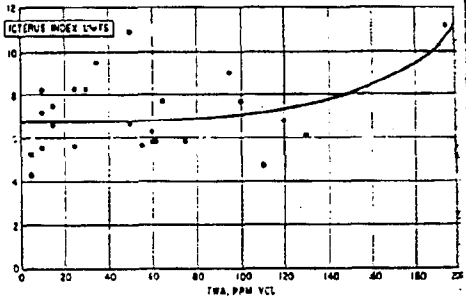

Figure 2. Regression model for icterus index.

Statistical Significance of Models

An appropriate question is: What measures of precision can be attached to the regression models? Three useful indices are the standard error of regression, Se, the overall F-Statistic, and the coefficient of multiple determination.

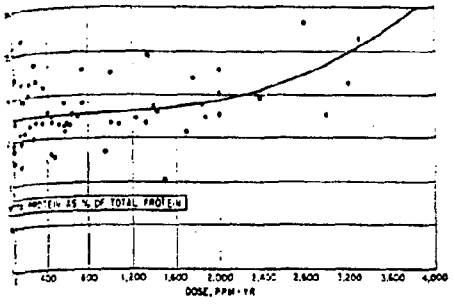

Figure 3. Regression model for beta-protein.

F. These measures of the "goodness of fit" for ach model of the clinical variables are listed Table VI. All of the regression models are ignificant at the P=0.001 level, except the cterus Index model, which is significant at the P=0.03 level.

Utility of the Models

The regression models must be used with scretion. Since the least square regression efficients are adjusted for other variables in e regression procedure, attempting to redict the response by changing only one ariable arbitrarily may be misleading. ecause of this, we must specify the prediction nge for each variable under investigation. ch prediction ranges are shown in Table II.

To relate the statistical results to the ctical question of an industrial hygiene standard requires careful consideration. First, an acceptable workroom air concentration must allow for men working in the environment for an entire career, up to 45 years; our data are useful only over a 20-year span. For effects which are cumulative, as most of those isolated in this study apparently are, the last part of a man's career is the limiting consideration. In view of our data and their ranges, we can examine the clinical variables at TOJ=20, and Age=60, the highest legitimate values of our predictive parameters. In the case of blood pressure, obesity must be fixed also if we are to predict the effect of the level of exposure, TWA. For this purpose, we hold "OB" constant at 1.06, the overall mean for the blood pressure data. The following functions result:

Systolic Blood Pressure
$$=136.80 + 0.034035\ (TWA)$$
Diastolic Blood Pressure
$$=84.74 + 0.018845\ (TWA)$$
Bromsulphalein
$$=2.12 + 0.034599\ (TWA)$$
Icterus Index
$$=6.82 + 0.000000002309522\ (TWA)^4$$
Hemoglobin
$$=13.97 - 0.0000000457339\ (TWA)^3$$
Beta-protein
$$=14.15 + 0.000001371545\ (TWA)^3$$

These clinical changes are tabulated in Table VIII as a function of TWA.

Discussion of Clinical Changes

In reviewing Table VIII, we note six factors which relate empirically to exposure. Within

TABLE VI

Statistical Significance of the Regression Models

Model	Number of Observations	Standard Error of Regression	Overall F-Statistic	Coefficient of Multiple Determination
Systolic blood pressure	98	12.9	24.53 (3;94)*	0.180
Diastolic blood pressure	98	7.6	39.46 (2;95)*	0.193
Bromsulphalein	65	1.5	43.85 (1;63)*	0.407
Icterus index	25	1.6	5.66 (1;23)**	0.191
Hemoglobin	83	0.83	8.95 (2;80)*	0.162
Beta-protein	58	2.6	12.65 (1;56)*	0.170

*P < 0.001
**P = 0.03

the scope of this study the predicted blood pressures, systolic and diastolic, did not rise to levels which would be considered abnormal. The hemoglobin, though statistically decreased, does not fall outside the normal limits for our laboratory. The significance of the change in ratio of the beta-protein is not known. We are left with two factors which give some cause for concern. The changes in the Icterus Index and in the BSP lend some support to the hypothesis that some changes in liver function have occurred in a few individuals exposed at the higher levels. The BSP appears to be most significantly correlated with exposure.

Within the study group were several individuals who, after approximately 20 years of exposure with time-weighted exposures of approximately 300 ppm of vinyl chloride and smaller amounts of vinylidene chloride during the early part of their careers, demonstrated a tendency to develop changes in certain laboratory tests which appear to be related to their exposure. Reference to Figures 1-3 indicates that our interpretation of the clinical changes must be tempered by the fact that only a small number of individuals experienced the highest exposures.

Two of the individuals showing the highest rise in BSP were rechecked in 1968. One had essentially normal laboratory findings and the other showed persistent elevation of various liver function tests, even though both had been removed from further exposure since 1965. The individual whose liver function tests remained elevated had a history of hepatitis preceding his exposure, although his pre-exposure liver function tests had been normal. Whether his abnormalities represented a result of his exposure or independent sequelae of hepatitis cannot be ascertained. Certainly it would be desirable not to consider individuals with a history of hepatitis as candidates for prolonged exposure to vinyl or vinylidene chloride. Unfortunately, since many cases of subclinical hepatitis occur, there may always be some individuals in a working population who have had hepatitis.

For most individuals in the study, the highest exposure occurred in the early phases of their careers and their later exposures were much lower. In the final analysis, much weight had

TABLE VII

Means, Standard Deviations and Limits for Clinical Tests

	Age				TOJ				TWA			
	Mean	SD	Limit		Mean	SD	Limit		Mean	SD	Limit	
Systolic blood pressure	128	14	188		40	10	65		10	5.0	25	
Diastolic blood pressure	81	8	109		40	10	65		10	5.0	25	
Bromsulphalein	3.3	1.9	9.4		41	11	65		11	5.3	25	
Icterus index	7.0	1.8	11.1		40	7.1	52		14	5.7	25	
Hemoglobin	14.5	0.9	16.4		40	10	64		9.4	4.8	20	
Beta-protein	14.7	2.9	22.6		42	10	65		12	5.0	23	

	TWA		
	Mean	SD	Limit
Systolic blood pressure	80	75	375
Diastolic blood pressure	80	75	375
Bromsulphalein	75	70	340
Icterus index	55	45	200
Hemoglobin	70	70	315
Beta-protein	60	50	200

TABLE VIII

Expected Response of Clinical Tests as a Function of Career TWA

Test	TWA, PPM Vinyl Chloride						
	0	50	100	150	200	250	300
Systolic blood pressure (Age = 60, OBES = 1.06)	136.8	138.5	140.2	141.9	143.6	145.3	147.0
Diastolic blood pressure (Age = 60, OBES = 1.06)	84.7	85.7	86.6	87.6	88.5	89.4	90.4
Bromsulphalein (TOI = 20, Age = 60)	2.1	3.8	5.6	7.3	9.0	10.8	12.5
Icterus index	6.8	6.8	7.0	8.1	11.0	X	X
Hemoglobin	14.0	14.0	13.9	13.8	13.6	13.3	12.7
Beta-protein	14.1	14.3	15.5	18.8	25.1	X	X

X = beyond range of available data

to be placed on the readings observed for those employees who experienced high exposure levels, especially during the period 1950-58. For example, the average time-weighted exposure level in 1950 was 155 ppm, whereas the average exposure level in 1965 was 30 ppm.

Our findings suggest that repeated exposure to vinyl chloride at TWA levels of 300 ppm or above for a working lifetime together with a very low level of vinylidene chloride may result in slight changes in certain physiologic and clinical laboratory parameters. The possibility of some impairment in liver function tests must be considered, even though no overt clinical disease was evident in any of the individuals studied. We shall continue our study, but suggest that similar studies to help clarify the effects of this material be performed for other worker populations exposed to vinyl chloride alone.

Conclusions

The present study offers a technique of judging exposure effects on a group of exposed workmen based on an analysis which is intended to account for individual levels of exposure rather than relying on a collective comparison with a so-called "control" population. The "exposed" group, especially when it is drawn from an industrial setting, will contain individuals subject to a wide range of exposures, and the mean clinical indices for the group may well mask significant individual differences within the exposed group that could be detected only by intra-group analysis.

We have attempted to correlate the clinical manifestations of a group of men for which exposure data as well as clinical measurements were available. With this approach, the "exposed" group will contain some individuals whose exposures are low enough to serve as "controls." The regression technique we have employed treats the exposure levels (Dose and TWA) as independent variables, thereby providing an open format that allows inclusion of any degree of exposure, including none. The advantage of regression analysis in this application lies in the ability to extract more substantial information on acceptable exposure levels by relating measured clinical changes directly to measured exposure. To use this method, good environmental and medical data must be gathered and consolidated concurrently in substantial quantity.

We have demonstrated the use of this statistical technique with a group of men exposed to vinyl chloride and trace levels of vinylidene chloride. In so doing, we have found some interesting apparent effects from chronic exposure to that system but, more importantly, the methodology looks promising as a needed improvement in our quest to make

practical use of toxicological feedback from worker exposures. We hope that others will offer further refinements and suggestions that will help attain this goal.

Acknowledgments

We wish to acknowledge the assistance of other members of the Medical Department and Environmental Research Laboratory of The Dow Chemical Company who, over two decades, gathered the basic information which has made this study possible. Our special thanks to go Mrs. Shirley Walker, R.N., who conditioned much of the medical data, to M. Gerald Ott for his suggestions with the statistical strategies, and to our supervisors and colleagues for their steady support.

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Course on Effects of Nonionizing Radiations

The Massachusetts Institute of Technology will present a special two-week program on Biological Effects and Medical Applications of Nonionizing Radiations, July 31-August 11, 1972. The course will present the basic physics, biological effects, biomedical applications and hazards of ultrasound, laser, microwaves and magnetic fields. Presentation will be in manner to be suited to individuals with clinical and physical science backgrounds. The information will also be related in context to the activities of the Federal Regulatory Agencies. Detailed information is available from the Director of the Summer Session, Room E19-356, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.

Such particles are found in "quartz-typical cells" very rarely or not at all. The authors make no definite statement that the particles are PVPNO, but if they are, they were not stained by hematoxylin-eosin, aniline blue, silver impregnation or Perl's stain. Weller and Ullmer (Ann. N.Y. Acad. Sci. 200, 624-632, 1972) mention only the presence of foam cells.

I should recommend to try the Ammon-Mohn technique in PVPNO.

3. Polyvinyl chloride (PVC)

There is an enormous technical literature on polyvinyl polymers; PVC is not mentioned in the last 4 years of Medical Abstracts and I could not find any biomedical titles in Chemical Abstracts. However, Dr. Volkheimer has studied PVC particles and their persorption (see G. Volkheimer's monograph "Persorption" G. Thieme Verlag, Stuttgart, 1972). On p. 7 the PVC particles (globules) are depicted.

The elimination of PVC globules (5-110 µm diameter) in the urine was detected already 1 hour after oral administration (Volkheimer et al., Deutsch. Gesundh. 20, 21-28, 1965). PVC caused also liver damage (personal communication) apparently unusual cell proliferations surrounding the globules. I don't know yet whether this observation has been published by the investigating pathologist; Volkheimer also told me that he did not succeed in staining PVC. Since colored

plastics exist, also PVC derivatives, e.g. CaNa poly-(vinyl methyl ether-maleate) one may have to try histological staining procedures. The above named co-polymer is widely used in dental practice for fastening dental plates etc. and may easily be ingested.

The monomer vinylchloride (VC) is a gas and is unlikely to form cell inclusions. Its toxic effect is evaluated by studying the cell injury. Publications on histochemical work have still to be checked; in the recent paper by Marsteller et al. (Deutsch. Med. Wschr. 98, 2311-2319, 1973) cytoplasmic inclusions of liver cells are not mentioned.

Letters

Letters, if clearly marked "For Publication," will be published as space permits and at the discretion of the editor. They should be typewritten double-spaced, with five or fewer references, should not exceed 500 words in length, and will be subject to editing. Letters are not acknowledged.

Polyvinyl Chloride in Fires

To the Editor.—The article "Polyvinyl Chloride Toxicity in Fires" by Dyer and Esch (235:393-397, 1976) contains a number of factual errors and certain misleading inferences.

In three places, the combustion of polyvinyl chloride (PVC) is said to produce chlorine and phosgene. In fact, these two materials have never been demonstrated to occur in the pyrolysis or combustion of PVC (*Journal of Polymer Science* 8:1887-1890, 1970; *Journal of Applied Polymer Science* 13:377-391, 1969; *British Polymer Journal* 3:186-193, 1971; *Journal of Applied Chemistry* 17:366, 1967). The authors point out, correctly, that hydrochloric acid and carbon monoxide are the main toxic combustion products of PVC but tie these to possible toxic synergy with chlorine or phosgene. It is wrong to raise the specter of toxicants which are not really there. In another instance, vinyl chloride is said to be produced. In work by Boettner et al (*Journal of Applied Polymer Science* 13:377-391, 1969), vinyl chloride was found in the combustion products of PVC corresponding to about 0.02% to 0.06% by weight of the original polymer. Carbon monoxide and HCl were formed at about 45% and 58%, respectively. The vinyl chloride was thus present at a tiny fraction of the primary toxicants and may indeed represent residual vinyl chloride from the original polymerization. The present-day levels of residual vinyl chloride in PVC are .01 or less the levels typical in 1969, when Boettner's work was done. Thus, whether vinyl chloride is a combustion product needs confirmation.

A discussion of the fuel loading in fire situations owing to the presence of plastics carries the statement that ". . . plastics posses a heat of combustion 2½ times that of other combustibles." The matter is not so simple. According to the National Bureau of Standards (*Modern Plastics* 52:81-82, 1975), the heats of combustion of PVC and some common materials, including other plastics, are

Cotton	7,122 BTU/lb
PVC	7,720 BTU/lb
Wood	8,825 BTU/lb
Wool	8,972 BTU/lb
Polyester fiber	9,300 BTU/lb
Polyurethane	16,000 BTU/lb
Polyethylene	20,050 BTU/lb

One can conclude from this that, on a pound-for-pound basis, PVC contributes less to fuel loading than many other materials in common use. The assignment of a flat 2½-fold factor for plastics over other materials in heat of combustion is, to say the least, misleading.

The authors cite work by Cornish and Abar[1] on exposure of rats to CO and HCl from pyrolysis in air or oxygen of pure and formulated PVC. This work pointed out that death from pure PVC pyrolysis was due to CO inhalation unless oxygen was added to the gas stream to keep carboxyhemoglobin blood levels low. It should be noted that when PVC formulated for wire insulation or floor tile was pyrolyzed, higher exposure levels were tolerated before death occurred. Thus, formulated PVC is apparently less toxic in fires than pure PVC and the former should be the subject of research rather than the latter, which is never used commercially.

The commercial impact of PVC is exaggerated. The 8.3 billion kg/yr stated as the annual production in the United States translates to 17.6 billion kg/yr in contrast to the 3.7 billion kg/yr actually estimated for 1975 for all uses. Roughly 123 billion lb/yr of lumber and plywood were used for construction alone. Upholstered chairs are not stuffed with PVC, as claimed in the article. Chair covering is often PVC-based; the stuffing is usually rubber, urethane, or a nonsynthetic.

We want to make it clear that we do not take lightly the potential problem that may occur from the combustion of articles made from PVC. We stress, however, the need for dissemination of accurate information. It's reasonable to think that society can cope with the true problem, accurately understood, as well as it has with the toxicity problems from conventional materials. That means a lot of work remains to be done to make both natural and synthetic materials safer to use.

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1. Cornish HH, Abar EL: Toxicity of pyrolysis products at vinyl plastics. *Arch Environ Health* 19:15-21, 1969.

Cardiac Care Units

To the Editor.—Frieden and Cooper (235:816, 1976) stated that "recent experiences with monitored cardiac care units have demonstrated that mortality can be reduced in the first few days after an acute myocardial infarction." However, critical review of articles on coronary care units fails to confirm a properly designed trial that supports that statement. Adler et al (*Br Med Bull* 30:242, 1974), in a review dealing with research on medical care, point out:

> Mortality within most coronary care units has declined over the years, but there has also been a parallel reduction in mortality in patients suffering from myocardial infarction, who are nursed in conventional wards (MacMillan & Brown, 1971). There is no evidence that hospitals play any part in altering the total picture of the disease.

In fact, the first randomized controlled trial comparing home care vs that in cardiac care units (Mather et al cited by Adler et al *Br Med J* 3:334, 1971) showed no striking difference in case fatality ratios between groups treated in the two settings.

There may be other impressive advantages to grouping patients, equipment, and trained personnel in one location within the hospital setting. Grouping makes sense. However, reduced case fatality ratios have not been demonstrated.

The conviction that cardiac care units are effective has been associated with the view that trials are not only unnecessary but unethical. It is unfortunate that rigorous evaluation was not carried out when units were first introduced, but British experience suggests that it is not too late to start.

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In Reply.—It is important to delineate the perspective in which a situation is viewed. It is generally agreed that the majority of cardiac deaths occur early and outside of hospitals. Our report and the reports of the cited authors deal with the subgroup of treated patients. I believe that one should first determine whether or not we are helping these patients. If we

Edited by John D. Archer, MD, Senior Editor.