Hydrocarbon exposure may cause glomerulonephritis and worsen renal function: evidence based on Hill’s criteria for causality

U. RAVNSKOV

Summary
Many observational and experimental studies point to hydrocarbon exposure as an important pathogenic factor in glomerulonephritis. The findings have made little impact on current concepts and patient care, possibly because the hypothesis of a direct causal effect of the exposure and the hypothesis that the exposure worsens renal function have not been considered separately. This review examines these two hypotheses using Hill’s criteria for causality. The results from 14 cross-sectional, 18 case-control studies, two cohort studies, 15 experiments on laboratory animals and two on human beings together with many case reports satisfy all but one of Hill’s criteria for both hypotheses. Of particular importance is the finding in the case-control and follow-up studies of an association between degree of exposure and stage of renal disease, and an inverse association between degree of exposure and renal function, indicating that the most important effect of hydrocarbon exposure is its effect on renal function. End-stage renal failure may be preventable in many patients with glomerulonephritis provided a possible exposure to toxic chemicals is discontinued.

Introduction
An association between hydrocarbon exposure and glomerulonephritis, the commonest cause of end-stage renal disease, was reported already in 1894.\(^2\) Up to 1975, the association was mentioned in sporadic case reports, but after the publication of the first case-control study by Zimmerman et al.,\(^3\) research has accelerated. Many case-control studies have now shown that a large proportion of patients with glomerulonephritis have had frequent and heavy exposure to hydrocarbons such as organic solvents, fuels, paints, glues and motor exhausts and the nephritogenic effect of hydrocarbons has been proved in several cross-sectional and experimental studies. However, most students of glomerulonephritis consider the association of minor importance, and very little about it is mentioned in textbooks. As the findings may have important implications for the prevention of renal failure in many patients, it seems worth presenting a summary of the accumulated evidence.

Hydrocarbon exposure may either initiate glomerulonephritis (hypothesis I) or worsen renal function (hypothesis II), or both. In previous studies, it has not been acknowledged that if a short but intensive exposure may suffice to initiate the disease in predisposed individuals, case-control studies are unable to falsify hypothesis I, because the total exposure of the patient may not necessarily exceed the exposure of most people. Instead, the temporality between exposure and start of disease should be studied. Hypothesis II is falsified, however, if studies of patients with chronic or end-stage renal failure cannot demonstrate a substantial exposure difference between patients and control individuals.

Address correspondence to Dr U. Ravnskov, Magle Stora Kyrkogata 9, S-22350 Lund, Sweden.
e-mail: uffe.ravnskov@swipnet.se
© Association of Physicians 2000
or if the total exposure is independent on renal function or stage of disease. In this paper, these two hypotheses are tested separately using Hill’s criteria for causality.

Methods
All case reports, cross-sectional studies, case-control studies, cohort studies and experiments with a design that allowed a test of the hypotheses, published before January 1999 in English, French, German and the Scandinavian languages, were included. Studies were sought in the Medline database, and for the period before 1964, in Index Medicus. Studies were also sought in the references of the above studies.

Results according to Hill’s criteria

Strength
Case reports
Many case reports have recorded an onset of glomerulonephritis closely related in time to exposure to organic solvents and other hydrocarbons. Most cases had end-stage renal failure at admission; a few were reversible. In two cases, the renal damage was reversible after discontinuation of the exposure without any other treatment; one of them a nephrotic syndrome recurred and disappeared several times in association with continuation and discontinuation of the exposure. Case reports are weak evidence, however, and a detailed review was therefore considered unnecessary.

An unexpectedly large number of the case reports concerned Goodpasture’s syndrome, a rare variant of glomerulonephritis. This is probably a result of selection bias, because a patient with bleeding in the lungs may well prompt the physician to ask about airborne toxic pollutants, compared to a patient with simple glomerulonephritis.

Cross-sectional studies
In at least 14 cross-sectional studies, workers exposed regularly to various hydrocarbons had urinary findings typical of early glomerulonephritis more often than did control individuals. The findings included an excretion of cellular sediment, albumin and/or transferrin, and glomerular antigens. In three of the studies significantly more exposed workers had renal failure.

Case-control studies
In a meta-analysis of the case-control studies, patients with glomerulonephritis had been exposed more often than control individuals in 17/18 studies. However, the difference was trivial in three studies and statistically significant in 11 only. This finding seems unsatisfactory, but if hypothesis II is considered separately, the negative case control studies were in fact supportive, because they included acute or early cases only or a subgroup with renal failure and significant exposure. Thus, after exclusion of three studies with 5–17% drop-outs due to death, the odds ratios (OR) for exposure in patients with acute or early chronic glomerulonephritis, patients with chronic renal failure, and patients with end-stage renal failure were 0.95, 3.1, and 5.9, respectively. In accordance, renal failure at follow-up, recorded in four studies, was seen mainly in patients with heavy or prolonged exposure, and improvement was seen only in patients who had discontinued the exposure. That OR for exposure was considerably lower in the studies with many drop-outs due to death (OR 1.6; 1.2–2.0) than in studies with 1% drop-outs or less (OR 3.7; 3.0–4.6) is also in accordance with the hypothesis, because most patients with glomerulonephritis die from end-stage renal failure, and according to hypothesis II, end-stage renal failure should be associated with heavy exposure.

Cohort studies
Assuming that the incidence of end-stage renal failure due to glomerulonephritis is about 30/ million population/year, it has been calculated that to demonstrate a significantly higher incidence among exposed individuals, a sample size of at least 22 000 exposed individuals is required. None of the large cohort studies of workers with occupational exposure were supportive, but they included a substantial number with little or no exposure. More important, they used death from renal disease as the end-point. As end-stage renal disease predisposes to other fatal diseases, and as many patients with end-stage renal disease are treated with dialysis or kidney transplantation, the incidence of glomerulonephritis in these studies may be seriously underestimated.

In a cohort study of 50 patients with biopsy-proven glomerulonephritis followed for 7–8 years, 9/26 heavily exposed but none of 24 moderately or rarely exposed patients had end-stage renal failure at follow-up. In a similar study followed for five years, 21/29 patients with progressive renal failure, but only 5/39 patients with stable renal function, had been exposed to hydrocarbons. The renal function in the latter five improved when the exposure was discontinued.
As hydrocarbon exposure is ubiquitous, the rarity of glomerulonephritis is probably explained by a hereditary cofactor. Interestingly, exposed patients with membranous glomerulonephritis have an increased genotypic expression for microsomal metabolizing enzymes.29

Experiments

There is solid, experimental support for both mechanisms. In fifteen studies30–44 on guinea pig, rabbit, cat, mouse and at least four different rat strains, exposure of the animals to various hydrocarbons has produced most of the typical human subgroups of glomerulonephritis such as minimal change nephropathy,43 IgA,38 and anti-glomerular-baseament nephritis,39 mesangial,41,44 extracapillary,36,37 and focal proliferative glomerulonephritis,35–39 and focal glomerular sclerosis.42 Renal failure was produced in four of the five experiments that included a study of renal function,32,36,43,44 and all experiments that included urine analysis found heavy proteinuria12,34,36,37,42–44 and even the nephrotic syndrome.36,37

These experiments were more successful than the immunological models, because with few exceptions, experimental glomerulonephritis produced by immunological means alone have failed to produce more than trace or transient proteinuria. Severe renal damage was seen mainly when the animals were exposed to nephrotoxic chemicals also, such as mercury, gold, lithium or Freund’s adjuvant, or if they were injected with heterologous antibodies, an irrelevant model of human glomerulonephritis.45,46

Only two experiments on human beings were identified. In one of them,47 patients with glomerulonephritis were asked to discontinue their exposure. Although the renal function was lower and the blood pressure higher initially, the course was more favourable in the 15 patients who discontinued the exposure, than in the 15 who did not.

The other ‘experiment’ was unintentional. After ingestion of adulterated cooking oil mixed with aniline, oleoanilides and azobenzene, 842 patients were admitted to hospital. Four of them had glomerulonephritis with renal failure, a frequency which is at least 150 times higher than the incidence of end-stage glomerulonephritis in the general population.48

Consistency

The consistency is strong, as an association between exposure and disease, and/or between exposure and renal failure, has been found in all types of observational and experimental studies. The association appeared both from direct questioning about previous exposure and from the occupations of the patients.

Specificity

There is lack of specificity because hydrocarbons may cause other diseases, and glomerulonephritis and renal failure may have other causes. Hydrocarbon exposure is associated with most subtypes of glomerulonephritis. This lack of specificity is not contradictory, however, because, as seen in the animal experiments, each hydrocarbon may produce a specific type of glomerular damage.

Temporality

In the case-control studies, only exposure that had occurred before the first symptoms of glomerulonephritis appeared, or before the diagnosis was settled, was recorded. Thus, the exposure must be primary, and glomerulonephritis secondary. Likewise, the patients’ choice of occupation preceded their disease.49,50 Close temporality was demonstrated directly in the case reports5 and in the only case-control study that addressed this question.51

Biological gradient

Dose-response, e.g., an association between degree of, and odds ratio for, exposure, was calculated in seven of the case-control studies and was present in five.21 Dose-response was also seen in the animal experiments.33,34,36,40,41,44 The association between exposure and stage of disease, and the inverse association between exposure and renal function reflect a biological gradient.

Plausibility

According to current concepts, glomerulonephritis is thought to be caused by immune complex formation in the glomeruli. There is much clinical and experimental evidence, however, that in many cases tubulointerstitial damage may be primary and the glomerular formation or deposition of immune complexes secondary.45,46,52 Almost all the chemicals that have been associated with human glomerulonephritis are tubulotoxic, and many of them produce glomerulonephritis experimentally without evidence that immune processes participate.46 Furthermore, the renal function and course in glomerulonephritis is strongly predicted by the degree of tubulointerstitial damage, but not by the degree of glomerular damage,45,46 and the urinary excretion of low-molecular-mass proteins53 and N-acetyl-β-glucosaminidase,54 markers of tubular
cell damage, is increased in most patients with glomerulonephritis. However, although immunological mechanisms may not be directly causal, their participation is likely, because many hydrocarbons have unfortunate effects on the immune system.\textsuperscript{55} Experimental glomerulonephritis induced by maleic vinyl ether anhydride\textsuperscript{43} and carbon tetrachloride\textsuperscript{44} were ameliorated by steroid treatment or irradiation of the animals.

**Coherence**

No important clinical or epidemiological characteristics of glomerulonephritis are in conflict with the hypothesis. That glomerulonephritis is seen about twice as often in men as in women, and that new cases are rare after the age of retirement, are consistent with an occupational disease. Oil-producing areas, such as South Trinidad,\textsuperscript{56} Kuwait\textsuperscript{57} and Maracaibo in Venezuela,\textsuperscript{58} are known to have a high endemic incidence of acute, post-streptococcal glomerulonephritis; epidemics are frequent, and here the disease often progresses to renal failure,\textsuperscript{56,58} whereas the course usually is benign.

**Analogy**

Glomerulonephritis has been associated with exposure to other tubulotoxic chemicals such as gold, lithium and mercury, both experimentally and in man.\textsuperscript{45} The pathogenesis of glomerulonephritis has many similarities with that of pyelonephritis. Previously, chronic pyelonephritis was seen as a result of recurrent urinary tract infections. Follow-up studies of patients with such infections have shown, however, that bacterial infections do not harm the kidneys by themselves; most cases of chronic, non-obstructive pyelonephritis are caused by analgesic abuse, not by bacteria. Most cases of glomerulonephritis are acute or subacute and post-infectious; many are subclinical, and they rarely leads to renal failure. Even acute glomerulonephritis associated with toxic exposure may be benign, provided that the exposure is discontinued.\textsuperscript{51} Continued exposure may explain why some patients with acute glomerulonephritis proceed to renal failure, just as the regular use of certain analgesics may explain why some patients with acute pyelonephritis do.

Analgesic nephropathy was unrecognized for many years because patients often denied their misuse. Patients with glomerulonephritis may deny exposure to hydrocarbons, not because of shame or guilt feelings, but because they have forgotten the exposure, or because they are not aware of it, or because many nephrologists are unfamiliar with the working conditions of their patients and do not know the relevant questions to ask.

**Conclusions**

In previous studies and reviews, most discussions have concerned possible bias that may have distorted the results, and rightly so. But attention should also be paid to the striking consistency of the findings. With one exception, all of Hill’s criteria for causality (Table 1) have been fulfilled for both hypotheses, and as stressed by Hill, lack of specificity should not be overemphasized if other, more important criteria are in accordance. Also, the unsupportive case-control studies, that have raised

| Table 1 | Summary of the evidence using Hill’s criteria for causality\textsuperscript{1} |
| --- | --- | --- |
| Hills criteria | Hypothesis I satisfied | Hypothesis II satisfied |
| **Strength** | | |
| a. Cross-sectional studies | Yes\textsuperscript{7,20} | Yes\textsuperscript{11,16,20} |
| b. Case-control studies | Yes\textsuperscript{49} | Yes\textsuperscript{11} |
| c. Cohort studies | | |
| Healthy individuals | No studies available | No studies available |
| Patients with nephritis | Not applicable | Yes\textsuperscript{37,28} |
| **Experiments** | | |
| a. Animal experiments | Yes\textsuperscript{30,44} | Yes\textsuperscript{32,35,41,42} |
| b. Human experiments | Yes\textsuperscript{49} | Yes\textsuperscript{15,46} |
| Consistency | Yes | Yes |
| Specificity | No | No |
| Temporality | Yes | Yes |
| Biological gradient | Yes\textsuperscript{13,14,36,40,41,44} | Yes\textsuperscript{22} |
| Plausibility | Yes | Yes |
| Coherence | Yes | Yes |
| Analogy | Yes | Yes |
doubt about the role of hydrocarbon exposure, were in fact supportive because they included only acute or early cases, or they had unexposed patients with normal or near normal renal function and exposed patients with renal failure. Many questions about the pathogenic mechanisms are still unanswered, but the therapeutic implications are obvious. If renal failure is a consequence of prolonged exposure to hydrocarbons, identification and elimination of that exposure, preferably in cooperation with experts in occupational medicine, should benefit the patient.

A systematic inquiry about toxic exposure in all patients with renal disease may prevent end-stage renal failure in many patients, because even for one study with 17% drop-outs due to death,59 exposure to hydrocarbons was recorded in 57–82% of the patient groups with end-stage renal failure,59,60,61 and such exposure seems to be important also in diabetic nephropathy and renovascular disease.62,63 Furthermore, exposure to other nephrotoxic chemicals such as chromium, welding fumes, lead and silicon compounds seems to be common in a variety of renal diseases including both non-systemic and systemic glomerulonephritis.63,64

Chronic glomerulonephritis with renal impairment most often proceeds to end-stage renal failure, irrespective of treatment. If an elimination of toxic exposure in such patients could modify the course, it would not only benefit patients and society, but also become the strongest evidence that the exposure is pathogenic.

References


