the Prime Minister or Home Secretary: routine points of evolution in governmental procedure are dealt with on a much lower level in the corridors of Westminster.

Many of the matters concerning certification, disposal of the dead, and the coroners' duties, though important, have not changed for a great many years, and a further slight delay would not be catastrophic. There is, however, one section of legal medicine in Britain which is moribund, and unless resuscitation by some form of intensive care is rapidly applied it will expire never to be replaced. This is the small specialty of forensic pathology, which has got progressively smaller over past years until now it is only just maintaining its existence in the university medical schools. The small number of full-time forensic pathologists available for the police, defence lawyers, and the teaching of forensic medicine is growing smaller every year with retirements, deaths, and illnesses. Excluded from the National Health Services in 1948, ignored by the Home Office except for a derisory retainer, and shunned by many medical schools, their specialty has shrunk progressively owing to an almost total lack of new entrants. The few medical schools that tolerate a department of forensic medicine usually look upon forensic pathology as a public service rather than an academic discipline.

The Brodrick Report recommended that a financial contribution from central funds should be made to universities to support forensic medicine departments, partly to provide a pool of expert advice in criminal and civil matters and partly to relieve the present ignorance of newly-qualified medical graduates of their legal responsibilities—a matter which is causing the medical defence societies some concern. At a time when there is a rising violent crime rate, police forces are being reorganized, the forensic science laboratory service is being expanded, and there is an all-round increase in awareness of the need for more stringent law enforcement it is paradoxical that one of the keystones of criminal investigation—forensic pathology—should be allowed to slide into oblivion.

Unless someone in Whitehall blows the dust off the report soon, it will not be a question of "Whatever happened to Brodrick?" but "Whatever happened to forensic medicine?"

[1] Home Office. *Report of the Committee on Death Certification and Coroners*, Cmnd. 4810. London, H.M.S.O., 1971.
[2] Home Office. *Report of the Departmental Committee on Coroners*, Cmnd. 5070. London, H.M.S.O., 1936.
[3] B.M.A. *Deaths in the Community*. London, B.M.A., 1964.
[4] Havard, J. D. J., *The Detection of Secret Homicide*, Cambridge Studies in Criminology, Vol. XI, 1960.

Vinyl Chloride and Cancer

The possible association between three cases of angiosarcoma of the liver and exposure to vinyl chloride (CH_2 CH_1 Cl) has received considerable coverage in the press.[1 2] Angiosarcoma of the liver is a very rare disease, there being about 20 to 25 cases a year in the whole of the U.S.A. The American industrial concern B. F. Goodrich and Co. was therefore alarmed[3] to discover that in one of its factories where vinyl chloride was used there had been one death from angiosarcoma of the liver in 1971 and two in 1973. These men had worked with vinyl chloride for 15-28 years. Two further cases of this form of cancer have since been reported[4] among vinyl chloride workers, one in the U.S.A. and one in Britain. These tumours have come to light only because they arose in an uncommon site for tumour induction in man. Had they occurred in a tissue which more frequently gives rise to cancer—for example, in the colon or lung—they would not have been considered significant as an indication of possible occupational cancer.

In addition to the possible neoplastic lesions workmen chronically exposed to vinyl chloride monomer may develop a sclerotic syndrome.[5] This includes sclerotic changes in the skin, with circulatory disturbances, osteolysis, thrombocytopenia, marked fibrosis of the portal tract, and sometimes impaired liver function. Oesophageal varices and pulmonary insufficiency with signs of pulmonary constriction may be present in some patients. Lange *et al.*[5] have suggested that this be called vinyl chloride disease.

The discovery of a cluster of cases of a rare tumour among workmen in a particular industrial process strongly resembles the original observations of bladder cancer induced by certain aromatic amines[6] and of scrotal cancer induced by soot.[7] Now, as then, much needs to be done before the association can be proved or disproved. Further cases need to be found if the association is to be strengthened. Vinyl chloride monomer is only one of the many chemicals used in the plastics industry, and it is possible that other contaminants of the working environment may play a part in the induction of these tumours. Properly conducted retrospective and prospective epidemiological surveys must be made; the first retrospective survey is already under way. Experiments on animals originally suggested that vinyl chloride is carcinogenic on the grounds that 17 out of 25 rats given 30,000ppm of vinyl chloride in the air for four hours a day five days a week developed[8] tumours of the "skin" and (to a lesser extent) possibly of the lungs and bone tissue (osteochondromata). The skin tumours were later diagnosed as arising in the acoustic duct, a fairly frequent site for induced tumours in rats. Workers in Europe and America have reproduced the induction of acoustic duct tumours and produced evidence that rats develop both angiosarcoma of the liver and nephroblastoma in response to treatment with vinyl chloride monomer. The minimum effective dose in the air appears to be between 250ppm and 50ppm. Man may respond to higher or lower doses than these rats—as may other species currently under test.

Meanwhile, responsible firms are warning their workpeople of the possible hazard and doing their utmost to reduce atmospheric levels of gaseous vinyl chloride monomer in the workplace to the lowest levels possible. The current threshhold limit value of 200ppm in the United Kingdom is higher than the 50ppm recommended by Dow Chemicals Inc., and it is clear that if vinyl chloride monomer is carcinogenic to man very much low r levels will have to be enforced. The past three decades h. ve seen both great advances in chemical engineering technique and an increasing awareness of the undesirability of exposing men to noxious vapours, so that the exposure to vinyl chloride monomer today may be only a fraction of what has occurred in earlier years.

The manufacture of polyvinylchloride takes place in three stages. Vinyl chloride monomer made by the reaction of the gases, ethylene and chlorine, first passes to the polymerization plant, where it is mixed with water, a plasticizer, and a catalyst and reacted under pressure in an autoclave to produce a slurry of polyvinyl chloride. This slurry is dried and further processed to give a powder. Exposure of the workman is greatest at the time of opening and cleaning the autoclaves, and it is at this point that the most stringent precautions appear to be required.

The public is exposed only to the polymer, polyvinyl-

chloride (PVC), a ubiquitous plastic. PVC should not be regarded as a carcinogen and should in normal use be safe. Tumours induced[9] by implanting films of polyvinylchloride (and many other plastics or metals) into the subcutaneous tissue of rats and mice have been shown to depend on the uninterrupted area of the film[10 11] and not on its chemical composition, and there should be no cause for public anxiety. On the other hand, PVC contains traces of monomeric vinylchloride, which may be liberated on heating, so that it is essential to ensure that in processing the material the concentration of the monomer should be kept to the lowest level possible.

New forms of industrial cancer are likely to be a recurrent problem until some way is found to screen both the old and the many new substances coming into commercial use each year. It is not feasible to look at all these substances by classic carcinogenicity tests in rats or mice: firstly, there are not enough trained personnel or facilities; secondly, relatively few substances are produced on a sufficient scale to justify the considerable expense of these animal tests; and, thirdly, industrial chemicals are seldom pure and carcinogenic impurities may vary from batch to batch.

What is now needed is a series of simple inexpensive tests which will indicate at least the more potent carcinogens. Such tests are being developed using as their endpoint mutagenesis of micro-organisms in vitro and, in vivo, unscheduled synthesis of DNA, transformation of cells in vitro, and so forth. Until these tests can be brought to a high degree of perfection and are then used systematically by industry we may expect to experience many more rude awakenings to possible industrial carcinogens.

[1] *Wall Street Journal*, 24 January, 1974, p. 4.
[2] *The Times*, 30 January, 1974, p. 3.
[3] *Chemical and Engineering News*, 28 January, 1974.
[4] *Guardian*, 31 January, 1974, p. 5.
[5] Lange, C. E., Jühe, S., Stein, G., and Veltman, G., *Internationales Archiv fur Arbeitsmedizin*, 1974, 32, 1.
[6] Rehn, L., *Langenbecks Archiv für klinische Chirurgie, vereinigt mit Deutsche Zeitschrift fur Chirurgie*, 1895, 50, 588.
[7] Pott, P., *Chirurgical Observations*. London, Hawes, 1775.
[8] Viola, P. L., Bigotti, A., and Caputo, A., *Cancer Research*, 1971, 31, 516.
[9] Oppenheimer, B. S., Oppenheimer, E. T., Danishefsky, I., Stout, A. P., and Eirch, F. R., *Cancer Research*, 1955, 15, 333.
[10] Alexander, P., and Horning, E. S., in Ciba Foundation Symposium: *Carcinogenesis: Mechanisms of Action*, ed. G. E. W. Wolstenholme and M. O'Connor, p. 12. London, Churchill, 1959.
[11] Nothdurft, H., *Naturwissenschaften*, 1955, 42, 106.

Fever in Malignant Disease

The Pel-Ebstein relapsing fever of Hodgkin's disease, so well remembered for some curious reason by generations of medical students, has never been quite the same since Richard Asher in his 1959 Lettsomian Lectures[1] shocked and amused his audience by doubting its very existence. It is certainly rare. In 124 febrile episodes experienced by 44 patients with Hodgkin's disease it was seen only once,[2] and a new review[3] of the causes of pyrexia of unknown origin does not even mention it. Nor does an excellent account of fever of unexplained origin in cancer patients, a contribution from Brussels in a recent number of the *European Journal of Cancer*.[4]

Unhappily for those who aspire to make a spot diagnosis from an examination of the temperature chart, it seems that neither the character nor the severity of the fever are of any help when it comes to deciding whether the cause is a malignancy itself or an associated infection.[2 5] The distinction is important, since untreated infection can be fatal in those who might otherwise be restored to temporary health or even cured of their cancer.[4 6] It is an equally serious error to give antibiotics when appropriate treatment for the malignant disease is what is needed to abolish the fever.

Carcinoma of the kidney (hypernephroma) is often thought of as the typical example of a tumour causing fever, but Berger and Simkoff[5] found that it caused a pyrexia of unknown origin in only 7 (2.5%) of their 273 cases, though 16% had some fever. About 20% of children with Wilms's tumour (nephroblastoma) are said to show fever at an early stage.[6] Ewing's tumour of bone may show fever,[12] and this can be a diagnostic trap if the radiographs suggest osteomyelitis. Primary or secondary malignant disease in the liver is another cause,[9 10] and a liver scan[11] or needle biopsy[3] may help in the diagnosis—and may reveal one of the other liver diseases causing fever of unknown origin.

A raised temperature is very common in acute leukaemia,[13] especially if the disease is untreated, or in relapse,[4 6] or if there is severe neutropenia;[4 14] but opinions differ as to how often it is due to associated infection. Immature neutrophils can kill bacteria but are less efficient.[15] In myeloma and chronic lymphatic leukaemia fever should always be assumed to be due to infection, host resistance being impaired in both conditions.[3 6]

In general, apart perhaps from newly diagnosed Hodgkin's disease, it is safest to suspect prolonged fever of being due to occult infection. Fever caused in some mysterious way by the tumour itself is important but uncommon. Even 50 years ago, when pyrexia occurred more often in hospital patients than it does today, Briggs[7] reported that half of his 238 patients had some fever but that in only 3% was it a symptom of any importance.

The fever of Hodgkin's disease (unlike pruritus, which is no longer considered a bad prognostic sign) is certainly an unfavourable feature[2 16 17] and often means that visceral disease is present.[4] Sokal and Shimaoka[18] carried out controlled experiments which showed that the urine from pyrexial patients with Hodgkin's disease induces fever in rabbits; they considered that an endogenous pyrogen was responsible. An important practical point is that the more advanced the Hodgkin's disease, and the more chemotherapy and radiotherapy the patient has received, the greater the chance that the fever is due to infection (often of the opportunistic kind), and this must be carefully looked for.[6 16]

The old idea that necrosis, ulceration, or infarction in the tumour is a sufficient explanation for fever in malignant disease has little to support it[10 19] But localized abscess or infection, sometimes masked by the tumour and not discovered until necropsy, is common. This accounted for 17 of the 27 patients reported by Klastersky and his colleagues[4] to have prolonged fever due to occult infection. In 9 of these 17 the local infection was thought to be the cause of death. In such cases the response to drainage may be dramatic, whereas antibiotics often fail.

Sometimes stopping antibiotics does more good than starting them; many dangerous infections (some fungal) are caused by endogenous organisms, encouraged to proliferate by the suppression of normal flora. In other cases a systemic infection is responsible, and here it is as well to remember that cancer patients are liable to all the infections that may cause fever in other people. The list of likely possibilities will vary in different parts of the world. What is true of Brussels or Birmingham may not apply in Brasilia or Bangkok. Two of the Brussels patients[4] were finally found to have (as well