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Introduction
From the pathologist’s viewpoint, most coroners’ necropsies are reasonably straightforward, particularly when an adequate history is available and a careful dissection is performed. Nevertheless, there will always remain a small proportion in which no obvious cause of death is apparent after detailed initial external and internal examination. It is this group with negative findings which is considered in this review.

Incidence
This is difficult to determine, but I suspect that most pathologists, if they were to be honest, would accept the figure of “about 5%” or “in the region of five to ten per cent” quoted by Knight, who also points out that, “autopsies reveal diseases and lesions that the person lived with and not necessarily those which killed him”. Coe also estimates that 5–10% of all sudden unexpected deaths show no gross anatomic cause of death at necropsy.

Personal approach to the problem
When a “negative” necropsy is encountered, four sequential steps (review, consider, rereview and conclude) are helpful. In more detail these are:

REVIEW EVIDENCE AVAILABLE
Although it is extremely foolish, and even occasionally dangerous, to begin a necropsy without as much background information as possible concerning the deceased and his or her death, it is often important actively to seek out further facts if the necropsy proves to be “negative”, and the pathologist must, therefore, “resort to the most important investigative tool of all, the telephone”.

History
Sometimes, discussions between the pathologist and the deceased’s general practitioner will reveal additional facts which may be relevant to the death but which were not provided initially by the investigating (particularly if junior and inexperienced) coroner’s officer—usually because their relevance was not appreciated by the lay police officer or by the family when interviewed by him. Examples include epilepsy (where sudden and unexpected natural death, without status epilepticus and often without any seizure is well recognised), insulin dependent diabetes mellitus (with risks of both hyper- and hypoglycaemia, the latter possibly being more likely in those using human insulin, as warning symptoms may be less pronounced), and cardiac arrhythmias due to isolated conduction system disorders (where there may be a history of palpitations or syncopal attacks, previous electrocardiogram abnormalities, or a positive family history). The importance of the history to the cause of death is discussed by Leadbeatter and Knight. When the death occurs in hospital, not only should all the case notes be available to the pathologist, but often, discussions with colleagues involved in the clinical management of the patient before death are invaluable, particularly in notoriously difficult cases—for example, death during or associated with general anaesthesia. Ideally, these colleagues should be present during the necropsy to permit a two way exchange of information and ideas, and it may well be prudent to arrange to perform the necropsy at a time which will allow them to attend.

Circumstances
Although all pathologists would agree with Polson, Gee, and Knight that “the major potential cause of mistakes is the approach to a post-mortem examination with a preconceived idea of the cause of death” based on the available medical history, most would be prepared to admit that their conclusions as to the cause of death have, on occasions, been influenced by the circumstances in which the body was found. The sudden death, while running for a bus, of a man seen clutching his chest and complaining of chest pain is unlikely to be other than natural, and this is bound to affect the pathologist’s assessment of the relevance of the diseases identified at necropsy.

CONSIDER FURTHER TESTS
Ideally, such tests should be carried out on most, if not all, coroners’ necropsies, but in practice this would be extremely wasteful of time and resources. Therefore, only a few cases are selected, and consequently mistakes are bound to be made. I am sure that I and all my senior colleagues must have missed deaths related to drugs, particularly in elderly persons with severe pre-existing natural disease, whose deaths aroused no suspicions of the investigating authorities. Further tests to be considered include:

Histology
This is a major aspect of the investigation of sudden death in infancy, where clinically
important infection may not be apparent on gross examination; such cases therefore require extensive histological sampling. Otherwise, although all pathologists would agree with Polson, Gec, and Knight that "histological examination of selected material should be an integral part of (all) post-mortem," experience dictates that histological analysis usually merely confirms the macroscopic findings and therefore proves unhelpful in difficult "negative" cases. Occasionally, however, unexpected relevant findings may come to the fore: these are usually in the heart, and the commonest is probably myocarditis.

Toxicology
This subject covers a vast area and includes drug interactions as well as deliberate and accidental overdoses. At the outset the initial requirement is to consider seriously that the death under investigation may be due to or modified by poisoning. If this possibility is not entertained appropriate specimens will not be taken or retained, and the correct diagnosis will be overlooked. It is always worth remembering that relevant clues may have been removed from the scene of death—deliberately by the deceased (after ingestion but before death) or by the family (either intentionally or inadvertently). Perhaps it is too melodramatic to expect that poisoning should be considered in every coroner’s necropsy, but if this were so, fewer cases would be missed. In this context the motto “be suspicious” is pertinent, not only to the pathologist but also to the investigating police (coroner’s) officer and the medical attendant visiting the scene of death. Even when poisoning has been considered and relevant specimens submitted to a laboratory for toxicological analyses, problems may still arise. A recent article discussing the serious and numerous problems of forensic toxicology and illustrating the types of mistakes which can and do occur makes interesting but depressing reading, particularly when words such as "abysmal", "blunders", "horrendous errors", "inexperience" and "incompetence" are used. In the light of this article how should the pathologist respond to a negative toxicology report, as it is obviously naive and quite wrong automatically to conclude that such a report inevitably excludes the possibility of poisoning? Should other substances be looked for by the same or a different laboratory, and if so, which substances and which laboratory? Should a greater emphasis be placed on the natural disease found at necropsy? Should the death be certified as unascertained? Of course, each case should be considered separately, but decisions in such instances are invariably difficult.

Microbiology or virology, or both
Relevant specimens for microbiological and virological investigation should be taken routinely in all sudden infant deaths and otherwise when considered appropriate. In most cases, however, such investigations provide important additional information, but they are unlikely to help with a “negative” necropsy.

Biochemistry
A range of biochemical substances can easily be analysed in post mortem blood, vitreous humor, and cerebrospinal fluid; some remain stable after death while others change reasonably predictably. “Normal” concentrations have been determined and are available together with guidance and discussions. Probably the most important and relevant analyses are glucose (to assist in the investigation of both hyperglycaemia and hypoglycaemia), urea (to determine the functional severity of renal disease and perhaps to assess dehydration), and electrolytes (particularly in infant deaths). Coe states that routine determinations of these substances in unexpected natural disease deaths yield significant results in over 5% of cases, and that in 3-6% the abnormalities are sufficient for incorporation into the formal death certificate. As in many other contexts negative findings may be as relevant as positive ones.

REVIEW EVERYTHING
Ultimately, the stage is reached when all available evidence has been collected and the results of all further tests are known. Hopefully, one or more investigations will have proved positive and the cause of death will be apparent; if not, it is necessary to review again all the information relating to the death and to ask several questions:

(i) How severe was the coronary artery atheroma? There is no doubt that coronary artery disease is responsible for most sudden and unexpected deaths in the community, and that it must be considered seriously in all such deaths. Davies and Popple in a widely quoted paper, believe that the minimum degree of disease reasonably associated with sudden death is at least one, and probably several areas of 85% luminal stenosis. Elsewhere in the same paper they state that “the least degree of coronary atherosclerosis which could reasonably cause death is one area of 75% stenosis”, but warn that evidence of the circumstances of the death is important, because an equivalent degree of disease can occur in many “control” subjects. Most pathologists would accept their conclusions: serious interpretational problems arise when the degree of stenosis is only 70% or even 60%, but where the circumstantial evidence is pointing strongly towards death from myocardial ischaemia. In such cases it is wrong to generalise, but I am sure that all senior pathologists have occasionally accepted “substantially less” coronary artery atheroma “where the circumstances and lack of other lesions seem to make this a reasonable assumption.”

Two additional findings may also help to point towards a sudden ischaemic heart death—myocardial fibrosis (indicating previous infarction or chronic ischaemia) and pulmonary oedema which is more prominent in the upper lobes. Perhaps coronary artery
spasm is an important contributing factor in these deaths.19

(ii) Any other macroscopic cardiac abnormalities? Clinically important left ventricular hypertrophy, regardless of its cause, is associated with sudden death. Davies and Popple state that hearts over 550 g in total weight "have left ventricular enlargement of a degree to be reasonably associated with death", and that this "risk is greatest with pressure overload on the left ventricle as in aortic stenosis or systemic hypertension".24 When less severe left ventricular hypertrophy is present, moderate coronary artery atheroma (40–60% luminal narrowing) may be relevant, as these separate conditions may act together to produce fatal myocardial ischaemia; under these circumstances, Part II of the death certificate format is useful. Clinically important right ventricular hypertrophy is also associated with sudden death: it indicates established pulmonary hypertension and cor pulmonale, and is confirmed by focal pulmonary artery atheroma; examination of the lungs should establish the cause. Other macroscopic cardiac abnormalities worth considering at this stage are all the cardiomyopathies and the floppy mitral valve syndrome.

(iii) Is the heart normal macroscopically? Myocarditis is a recognised cause of sudden and unexpected death, and often no abnormalities are apparent macroscopically.29 When the histological features of myocardial fibre necrosis with interstitial, often perivascular, infiltration by lymphocytes, plasma cells, macrophages, neutrophils and eosinophils are extensive and florid, diagnosis is easy; serious interpretational difficulties do arise, however, when only very occasional tiny aggregates of inflammatory cells are identified.30,31 Perhaps such isolated lesions are more relevant to the cause of death when they are adjacent to conducting pathways, although I have seen them in an elderly man battered to death and a two year old child who was undoubtedly suffocated, and others have encountered such foci in those dying from obviously unrelated causes.32,33

(iv) Have any marks on the body been overlooked? Those most likely to be missed are from electrocution and needle punctures. When the domestic electricity supply is involved, the electric mark may be trivial and unassociated with a thermal burn; although it is most likely to be found on the hands, it may be anywhere on the body, including beneath intact clothing.11 Needle punctures can be difficult to identify, particularly in the absence of associated tissue bruising or if obscured by tattoos: although predominantly located in the antecubital fossae and forearms, they may be found anywhere, and areas around wrists, hands and ankles and groins should specifically be examined. It must be remembered that few National Health Service laboratories have the facilities to identify all the substances likely to be injected by such drug users, and it is therefore still worth checking for needle puncture marks, even when the local toxicology screen has proved negative. As deaths from both electrocution and intravenous drug abuse are invariably rapid, important clues should be apparent to investigators visiting the scene of death, but relevant features may have been overlooked, and it is always possible that the scene was "tidied up" by the relatives or friends who discovered the body.

(v) Could carbon monoxide poisoning be involved? Despite the impression created by several (particularly the smaller) textbooks of forensic medicine, not all the bodies of those dying from carbon monoxide poisoning show bright, cherry-red discolouration of post mortem lividity, internal organs, and tissues. Not infrequently, "asphyxial" changes predominate, and the lividity is intensely cyanosed, particularly when the build-up of carbon monoxide has been slow and insidious. Furthermore, relatively low saturation concentrations (25–30%) may be an important contributing factor in those with severe pre-existing natural conditions such as chronic obstructive airways and ischaemic heart diseases. As in other contexts, the circumstances surrounding the discovery of the body should alert the pathologist to specific possibilities, but carbon monoxide poisoning is always worth considering in any "negative" necropsy.

(vi) Would discussions with, or referral to colleagues assist? Most of us find that discussing problems with colleagues, whether senior or junior, is helpful when trying to crystallise ideas and form conclusions. With negative necropsies, a case review with a fellow pathologist is often valuable, not only because new ideas may be suggested, but also because difficulties will be understood and shared. Occasionally, discussions with other colleagues, such as a toxicologist when low, sublethal drug concentrations have been found, or a cardiologist when a cardiac conduction system disorder is suspected, are well worthwhile. Finally, it is worth considering referring the case to a specialist pathologist, such as a cardiac or neuropathologist, for an expert opinion.4

Draw final conclusions
By this stage all available evidence has been collected, the results of all further tests are known, and all aspects of the case have been rereviewed; no further information is likely to be discovered, and final conclusions must be drawn. The pathologist has to decide whether any one or more of the positive findings, either alone or in combination, is or are sufficient to have caused death; if so, death should be certified accordingly. I think that a decision to offer a definitive cause of death at this stage should be made positively and honestly on the facts available, and not simply to clear the case off the pathologist's desk. Such a decision should reflect the balance of probabilities or at least the "preponderance of evidence".4 On the other hand, there must be a readiness to "admit
defeat”), and not to assume some unwarranted cause of death, or to attribute meaning to meaningless findings. The pathologist must not overspeculate where facts do not justify conclusions, and he or she should be unwilling to offer an unsubstantiated opinion as to the cause of death. Under these circumstances, death should be certified as “unascertained”, a term understood and accepted by coroners, even though they may not “like a case to end in limbo as far as the cause of death is concerned”. There is no doubt that younger pathologists feel embarrassed or are afraid of being seen as incompetent when unable to provide a cause for death. Such natural responses should be allayed, because, as Knight rightly points out, “as the pathologist increases in experience and maturity, he is more ready to concede that he cannot find the cause of death, and this is more satisfactory”. The incidence of unascertained deaths inevitably varies widely among different areas and reflects the policies of local pathologists. According to Coe, “from 1 to 5 percent of all deaths investigated will remain unexplained in most good medicolegal investigative systems”. Most pathologists would find this estimate rather high, even if it were to include cases designated the “sudden infant death syndrome”—an extremely convenient, but scientifically meaningless entity. There is no doubt that most unascertained deaths are encountered in children and young adults. Like Knight, I strongly suspect that the very low incidence of such deaths in older persons is fallacious and merely reflects “the convenient overlay of degenerative diseases” which are inevitably found in such age groups and which are therefore used to provide the cause of death. Finally, I think it important to support Professor Knight’s view that in negative necropsies, “though every effort should be made to dis-cover the truth, truly negative findings should be recorded as such so that the way is left open for future revision if further facts come to light”.

This paper represents part of an invited address to the Coroners’ Society of England and Wales in Manchester, October 6, 1989.

7 Teuscher A, Berger WG. Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. Lancet 1987;i:382-5.