

Procalcitonin: how a hormone became a marker and mediator of sepsis

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Calcitonin was discovered in the early 1960s [1], at which time it was assumed to be a single hormone with a yet-to-be-determined role in human physiology. Since then it has been found to be only one entity among a large array of related circulating peptides, at least one of which has a pivotal role in the host response to mi-

crobial infections [2, 3]. The aim of this review is to describe this metamorphosis of an endocrine hormone to a new class of hormokine mediators in infectious diseases.

Key words: calcitonin; hormokines; sepsis

Calcitonin – a hormone seeking a job

Mature calcitonin (CT), named after its hypocalcaemic effect, was originally thought to be exclusively of thyroïdal origin and to play an important role in skeletal homeostasis [4]. However, provided that thyroid hormone is replaced, thyroidectomy in humans has few or no major pathological consequences: calcium homeostasis re-

mains largely intact and bone density is not affected. Thus, the basic dilemma remains that the physiological functions of mature CT in man are unknown; as yet, no disorders attributable to either an excess or a deficiency of mature calcitonin have been identified [5].

Calcitonin precursors: *the* markers of sepsis?

Critically ill patients often manifest a systemic inflammatory response syndrome (SIRS) independently of an infection (white blood count >12,000 or <4,000 cells/μl; heart rate >90 beats/min; respiratory rate >20 breaths/min; body temperature >38 or <36 °C). When SIRS is present and infection is proven or suspected, the term sepsis is used. The traditional clinical signs of infection and the routine laboratory tests in sepsis (e.g. C-reactive protein [CRP] or white blood cell count) are not specific and sometimes misleading. In severe infection, most classical proinflammatory cytokines (e.g. TNF-α, IL-1β or IL-6) are increased only briefly or intermittently, if at all. Despite the use of new treatment modalities [6], mortality in sepsis remains high, often due to delayed diagnosis and treatment. In view of this diagnostic and therapeutic dilemma, an unequivocal test for the differential diagnosis of infection and sepsis would be very useful.

In microbial infections and in various forms of severe systemic inflammation, circulating levels of *calcitonin precursors* (CTpr), including the prohormone procalcitonin (ProCT), increase several-

fold to several thousand-fold, and this increase often correlates with the severity of the condition and with mortality [2, 7–9]. Initially, calcitonin is biosynthesised as ProCT, a precursor which is cleaved enzymatically into free aminoprocalcitonin (N-ProCT) and the conjoined calcitonin:calcitonin-carboxypeptide-I (CT:CCP-I). The latter, in turn, is processed into free CCP-I and immature CT. The thirty-three amino acid immature CT is then amidated to yield the thirty-two amino acid mature CT (fig. 1). All these peptides are found in the serum of normal persons. However, in sepsis, with the exception of mature CT, they are increased to a more or less marked extent [10].

Several clinical studies have confirmed the superior diagnostic utility of serum levels of CTpr in sepsis and their greater reliability, compared to other markers, in following the course of illness (fig. 2) (references in [2, 11]). Importantly, in sepsis, the extent to which any specific CTpr peptide is increased relative to the others varies; indeed, the levels of N-ProCT and CT:CCP-I may be even higher than the ProCT values [10]. The

commercially available two-site assay (LUMitest® PCT, B.R.A.H.M.S. Diagnostica GmbH, Hennigsdorf/Berlin, Germany), measures both ProCT and the conjoined CT:CCP-I by means of a luminometer. This assay is useful in detecting markedly elevated CTpr levels in sepsis. However, the current assay has the disadvantage of relative insensitivity, with an accurate detection limit of ~0.3 to 0.5 ng/mL [8, 10]. A colorimetric bedside test (PCT®-Q, B.R.A.H.M.S. Diagnostica GmbH, Hennigsdorf/Berlin, Germany) has the advantage of providing rapid determination of circulating CTpr levels (in 30 minutes); however, the assay is only semi-quantitative and is not sensitive enough to detect mildly or moderately elevated CTpr levels [12]. Currently, the most sensitive assay capable of measuring CTpr in normal persons utilises an antibody to N-ProCT as the free peptide and within the ProCT molecule [8].

Clinically, the authors have found the determination of circulating CTpr levels to be very useful in complex, polymorbid cases with suspected bacterial infections. For example, serum CTpr measurement can be helpful in predicting the pres-

ence of serious bacterial infection in a patient with fever but without localising signs [13]. Another important use is in patients with meningeal irritation; in this context, elevated circulating CTpr levels are highly suggestive of bacterial infection [9, 14]. The CTpr assay can also be used where renal failure is present [2, 15]. In immunocompromised patients with AIDS or neutropenia, an ultrasensitive CTpr assay is probably more desirable [16–18]. In patients with haemodynamic shock, the finding of relatively low levels of serum CTpr suggests a non-bacterial cause (e.g. acute adrenocortical failure or haemorrhage) [19]. CTpr determination can also be useful in differentiating joint infections from autoimmune inflammation (e.g. rheumatoid arthritis) [20].

Whatever the initial triggering insult may be, markedly severe systemic inflammation *per se* may be reflected in increased serum levels of CTpr [11]. For example, whether or not bacterial infection has been found, moderate to marked serum CTpr increases occur in pancreatitis due to biliary obstruction or in association with necrosis, in chemical pneumonitis [21], in burns [7, 22, 23], in heat

Figure 1

Schematic illustration of the human calcitonin precursors (procalcitonin and its constituent peptides), which are found in the free form in normal human serum. Mainly in thyroidal C-cells, immature calcitonin is amidated into mature calcitonin by the enzyme peptidyl-glycine-amidating-monooxygenase (PAM). CCP-I denotes calcitonin carboxypeptidase-I. In sepsis these peptides are variably increased, often to very high levels. However, in this condition, serum levels of mature calcitonin remain normal or are only slightly increased.

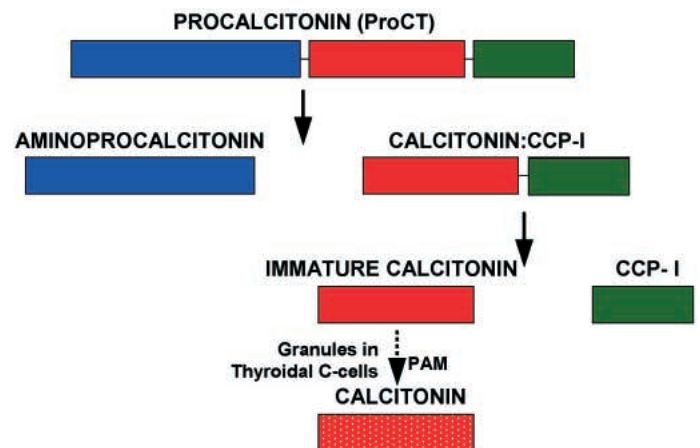
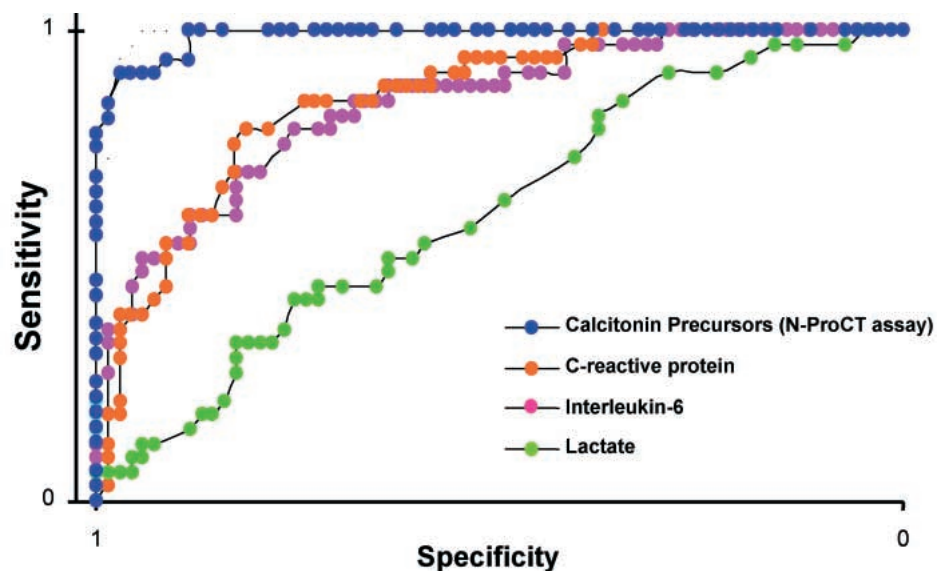


Figure 2

Diagnostic accuracy of sepsis markers. The serum CTpr assay is compared with circulating interleukin-6, C-reactive protein, and lactate measurements in critically ill patients with systemic infections (i.e. sepsis, severe sepsis, or septic shock) on admission. They are displayed in a receiver operating curve (ROC) analysis (adapted from [2]).



stroke [24], in mechanical trauma [25], and following surgery [26]. Additional studies are needed to determine whether the increased serum CTpr levels in such apparently non-bacterial insults are a manifestation of translocation to the blood stream of bacteria or bacterial products (e.g. endotoxin) from the gut [27, 28]. In this context administration of endotoxin to normal human volunteers increases serum CTpr values to levels seen in sepsis [29]. In addition to endotoxin, various proinflammatory mediators have also been shown to induce CTpr, e.g. TNF- α , IL-2 or IL-6 [30].

At least one parasitic infection (malaria) may substantially increase serum CTpr [31]. In fungal infections levels are occasionally [32], but not always [33], high. Viral infections may be associated with mildly or moderately elevated CTpr levels [14, 34], and here again bacterial translocation from the gastrointestinal tract may be a factor.

It is of interest that, physiologically, newborns also exhibit a considerable increase in circulating CTpr which reverses spontaneously in the first week [35-37]. This could be interpreted as a host response to initial establishment of the normal intestinal bacterial flora [38]. If the respective reference ranges are applied appropriately, CTpr can also be used to diagnose microbial infections in

newborns [39-41]. In these circumstances an ultra-sensitive CTpr assay would be preferable. Table 1 provides a detailed outline of the use and interpretation of serum CTpr determinations in clinical practice.

As to whether calcitonin precursors are *the* markers of sepsis, the answer is no. Some patients without apparent clinical symptoms of sepsis nevertheless present high serum CTpr levels, and some patients with a syndrome meeting the commonly accepted criteria for sepsis do not have high levels. Moreover, the clinical diagnosis of sepsis is often subjective and hence not infrequently uncertain. For example, a patient with SIRS and positive blood cultures clearly merits a clinical diagnosis of sepsis, while a patient with SIRS, consistently negative blood cultures and a localised bacterial infection (e.g. pneumonitis or pyelonephritis), may or may not be considered septic. Thus, *evaluation of the reliability of a marker for sepsis is contingent upon the accuracy of the clinical diagnosis*. A serum CTpr level must be evaluated with proper consideration of the clinical and laboratory context. Finally, whether or not SIRS is present, there is an overlap of serum CTpr values between patients with marked systemic inflammation and those with either a presumptive or definitive clinical diagnosis of sepsis.

Origin and regulation of calcitonin precursors in sepsis

CTpr emanate from the calcitonin I (CALC-I) gene on chromosome 11. In the traditional endocrine view, CT is produced mainly in neuroendocrine C-cells of the thyroid. In the absence of infection, the extra-thyroidal transcription of the CALC-I gene is suppressed and confined to selective expression in neuroendocrine cells found mainly in thyroid and lung. In these neuroendocrine cells, the mature hormone is processed and stored in secretory granules [4].

A microbial infection induces a ubiquitous increase in CALC-I gene expression and a constitutive release of CTpr from all tissues and cell types throughout the body [3]. Thus, under septic circumstances, the entire body could be viewed as an endocrine gland. Indeed, the transcriptional expression of CT-mRNA is more uniformly up-regulated in sepsis than are the mRNAs of the classical cytokines (e.g. TNF- α and IL-6). Interestingly, there is relatively low expression of CTpr in

white blood cells [3, 42]. The greater CTpr mRNA induction and CTpr peptide release from parenchymal cells compared to circulating cells appears to indicate a tissue-based rather than leukocyte-based host defence mechanism. Thus, the authors advance the hypothesis that CALC-gene products are a prototype of *hormokine* mediators and may follow either a classical hormonal expression or, alternatively, a cytokine-like expression pathway. The production of hormokines is mediated by as yet unknown factors and may be induced either directly via microbial toxins or indirectly via a humoral or cell-mediated host response. In sepsis, the predominance of CTpr as opposed to mature CT is indicative of a constitutive pathway within cells lacking secretion granules and hence bypassing of much of the enzymatic processing. Consequently, as is the case of most cytokines, there is very little intracellular storage of CTpr in sepsis [3].

The mediator of sepsis?

Similarly to what occurs in humans, CTpr are also increased in septic hamsters [43, 44]. In the hamster model of sepsis, ProCT does not initiate or enhance IL-1 β or TNF- α expression;

however, the massive and sustained elevation of this hormone seen in sepsis can be induced in normal hamsters by administration of the cytokine TNF- α . This suggests that ProCT could be a sec-

ondary mediator which may augment and amplify, rather than initiate, the septic response [45].

Both hypocalcaemia and increased serum levels of CTpr are common findings in intensive care patients, especially those with infection and sepsis. Indeed, ionised hypocalcaemia is more pronounced with increasing severity of infection, and occurs in parallel with the marked increase of CTpr [46]. In contrast, as mentioned above, serum levels of mature CT are normal or only minimally elevated in sepsis [8, 9, 46].

Importantly, CTpr contribute greatly to the *deleterious effects* of systemic infection. Administration of ProCT to septic hamsters with peritonitis doubled their death rate, which reached levels exceeding 90%, and treatment with ProCT-reactive antiserum increased the survival of septic hamsters [44]. In addition, one-hour intravenous *immunoneutralisation* using an antiserum reacting specifically with porcine ProCT improved the physiological and metabolic parameters of septic pigs and greatly increased their short-term survival (from 0% to 80%) [47]. Further, recent experiments have demonstrated that such immunoneutralisation is effective even when administered after the animals are moribund [48]. Studies have demonstrated that

what is beneficial is probably immunoneutralisation of the entire ProCT molecule. There are thus several observations to indicate that ProCT is not only a necessary precursor to the biosynthesis of mature CT but also, at the high concentrations occurring in the setting of sepsis, a potentially *harmful mediator involved in the septic response*.

Several characteristics of ProCT militate in favour of this hormokine molecule as a therapeutic target in sepsis. In contrast to the transiently increased classical cytokines, for which immunoneutralisation trials in humans have been disappointing, the massive increase in circulating CTpr persists for several days [29]. Moreover, CTpr is very frequently increased in overt sepsis, its onset is early (within 3 hr), and the diagnostic accuracy of the measurement should greatly improve patient selection for any study of the therapeutic efficacy of ProCT immunoneutralisation in humans.

As to whether procalcitonin is THE mediator of sepsis, the answer is no. ProCT is certainly not the be-all and end-all of this dreaded condition. But it certainly appears to be an extremely important mediator, the immunoneutralisation of which shows *significant therapeutic promise*.

How do CTpr, including ProCT, mediate their effects?

Molecular and animal studies are only beginning to unravel the pathophysiological mechanism of CTpr action in sepsis. In this disease, several CTpr are increased, including ProCT, N-ProCT, CT:CCP-I, immature CT, and CCP-I, any of which may have agonistic, antagonistic, or neutral effects [10, 45].

Also, several members of the *calcitonin gene family of peptides* comprise a functional unity [4]. The CALC-I gene, by alternative processing of the primary RNA transcript, gives rise to two different so-called mature peptides: calcitonin (CT) and calcitonin gene-related peptide I (CGRP-I). Like CT, CGRP-I is initially biosynthesised as a larger prohormone which is subsequently cleaved into smaller precursors. It is relevant that CGRP-II, amylin, and adrenomedullin, also members of the CT gene family of peptides, are encoded on the CALC-II, -IV, and -V genes respectively. In sepsis, mRNA for CGRP-I, CGRP-II and adrenomedullin also appear to be ubiquitously expressed [49]. Based on structural homologies, different members of these CT-gene family peptides have different profiles of bioactivity, which they exert by binding to the same family of receptors.

There are two subgroups of *receptors* for the CT-gene family: CT receptors (CRs) and CT receptor-like receptors (CRLRs). Each member of

the CT-gene family of peptides binds with differing affinities to these receptors. Accessory proteins act upon these receptors, thus altering their specific responsiveness and hence the physiological profile of action of the CT-gene peptides. These accessory proteins, which are called *receptor-activity-modifying proteins* (RAMPs), alter the receptors' phenotype; they act on the CRs by modification of their genes and on the CRLRs by influencing transport to the plasma membrane. The presence, concentration, and/or timing of one or more of the three RAMPs (RAMP-1, -2, and -3) determines the specific cellular phenotype of the receptor that is ultimately expressed on the cell surface [50]. The profile of RAMP expression and activity is altered by the local milieu and is subject to humoral influences. This elegant system allows for diversification of receptor function, and hence modulates the action of the CT-gene products according to ambient needs. Thus, both in health and disease, a response to different peptides of the calcitonin gene family of peptides occurs in a dynamic and varying manner [4]. Further studies are needed to determine whether high levels of circulating ProCT or other CTpr may blunt the effects of CGRPs and/or adrenomedullin, peptides which may otherwise be beneficial in sepsis.

Conclusions

Although a multitude of humoral substances are increased in patients with systemic infection, very few are reliable markers for the presence of the condition, its clinical course, the response to therapy or the prognosis. Several clinical studies have demonstrated the superior diagnostic accuracy in sepsis of circulating CTpr, including ProCT, as compared to all other markers. Their concentrations increase up to several thousand-fold in microbial infections, and this increase correlates with the infection's severity, course, and mortality. Thus, depending on the clinical situation and the sensitivity of the assay used, serum CTpr levels have very important clinical applicability for differential diagnosis, guidance of treatment, evaluation of response and prediction of outcome.

In addition to being a marker for sepsis, ProCT plays a critical role as a mediator in systemic infections and contributes markedly to the deleterious effects of systemic infection. It is an ex-

tremely potent actor in the pathophysiology of sepsis. Importantly, its ease of measurement and its prolonged persistence in the serum during sepsis mean that immunoneutralisation is possible either very early or later in the course of illness. Recently we showed that this therapy is effective even if the septic animal is moribund. Clearly, further elucidation of the biological actions of ProCT in sepsis will open up new therapeutic avenues for the treatment of this illness in humans.

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Table 1

25 clinical indications, guidelines and caveats for the interpretation of serum CTpr*.

The critically ill patient with sepsis and suspected bacterial infection should have a serum CTpr determination. In most such patients with marked bacterial infection, serum values will be high, and sepsis is diagnosed [2, 8, 9]. A lower level may indicate another cause of illness, though local infection may still be present.

In a patient with sepsis, the initial serum CTpr value may have prognostic significance (i.e. extremely high levels correlate with mortality) [51]. Similarly, a further later increase may presage a fatal outcome [52].

Very high levels of serum CTpr may occur in septic patients with severe SIRS and presumed infection, whether or not blood cultures are positive.

In a patient with demonstrated sepsis, a progressive decrease in an initially high CTpr commonly indicates a response to therapy, an improvement in the clinical course and a favourable outcome [26, 53]. In such circumstances, however, a more sensitive CTpr assay is usually required to evaluate significant day-to-day fluctuations and reliably detect meaningful trends.

In the elderly patient with recent onset of confusion, anorexia or incoordination, and for whom systemic bacterial infection is being considered, serum CTpr should be determined. Such patients are often normothermic or hypothermic, may not have leukocytosis, and may not manifest other signs of SIRS, such as tachycardia or tachypnoea. Furthermore, cultures in elderly patients may present positive urinary bacterial cultures and/or bacterial colonisation of the bronchial tree, without sepsis being present. If, however, sepsis is present, serum CTpr levels will be high.

In a febrile patient, serum CTpr levels may differentiate bacterial infection from other, non-infectious causes of fever in which serum CTpr levels will usually be considerably less elevated or normal (e.g. drug fever, sarcoidosis, familial Mediterranean fever, collagen-vascular disease, lymphoma, leukaemia, sarcoidosis, solid tumors such as hypernephroma, granulomatous thyroiditis, fever of unknown origin and factitious fever) [54, 55]. The diagnostic and predictive utility of serum CTpr assay in patients with neutropenic fever is uncertain [56].

Serum CTpr levels are considerably higher in patients with septic shock as opposed to those with cardiogenic shock or with shock due to haemorrhage or acute primary adrenocortical insufficiency [11, 19].

In the acute respiratory distress syndrome of adults (ARDS), higher CTpr levels occur if the cause is infectious than if there is a non-infectious aetiology. However, in acute respiratory distress syndrome of the premature infant, extremely high CTpr levels often occur without evidence of bacterial infection.

Serum CTpr levels are increased in most patients with pneumonitis [21]. However, if pneumonitis or pyelonephritis is minimal, SIRS may not be present. These patients may not have increased levels of CTpr when assayed commercially, but they often will have increased levels if an ultrasensitive CTpr assay is performed. This allows early identification of the problem and, if such values subsequently increase, permits the diagnosis of early sepsis. It will need to be determined whether the increased sensitivity of an ultrasensitive CTpr assay is accompanied by a decrease in specificity and positive predictive value.

In patients with long-term intravascular catheters (e.g. central venous pressure monitoring, renal dialysis, prolonged antibiotic therapy, chemotherapy, intravenous alimentation), a sudden increase in previously normal or only mildly elevated levels of CTpr often predicts, very early, the onset of bacterial sepsis; this diagnosis of sepsis may occasionally precede the appearance of a positive blood culture or signs of sepsis. However, for this purpose an ultrasensitive CTpr assay must be used.

Significant viral infections are usually associated with only minimal to moderate increases in serum CTpr; high levels strongly suggest bacterial super-infection. In meningitis, the high levels of CTpr encountered where the aetiology is bacterial will contrast markedly with the lower levels in the vast majority of those with a viral aetiology [9, 14].

Patients with AIDS without any associated bacterial infection do not exhibit increased CTpr as assayed by the current commercially-available assay [16]. However, an ultrasensitive CTpr assay does reveal moderate elevations.

In acute attacks of *Plasmodium falciparum* malaria, serum CTpr levels are markedly elevated; levels decrease with clinical improvement [31]. Most other parasitic infestations are not acute and have not been studied.

Table 1

Patients with systemic fungus infections (e.g. candidiasis, aspergillosis) may have increased serum CTpr values [32]. However, some patients have slightly or moderately increased levels [33, 57].
In severe mechanical trauma there is an early transient increase in serum CTpr. The level peaks within 1–3 days and is proportional to the severity of the tissue injury. Furthermore, a later secondary increase in CTpr is strongly suggestive of bacterial infection [25].
Following surgical trauma, serum CTpr shows an increase in the first 1–2 days, the level of which correlates positively with the extent of surgery [58]. After some surgical procedures a high day-one postoperative serum CTpr is predictive of mortality [59]. However, after cardiopulmonary bypass there is a particularly rigorous inflammatory cascade and marked early serum CTpr elevation does not necessarily indicate infection [60–62]. But here, as in any postoperative patient, either a persistently high serum CTpr level or a later, marked, secondary increase strongly suggests systemic bacterial infection [63].
In patients who have undergone heart, lung, heart-lung, or liver transplantation, high serum CTpr levels indicate bacterial infection rather than acute rejection [63, 64]. Importantly, administration of monoclonal or polyclonal anti-thymocyte globulin to treat acute rejection induces a marked increase in circulating CTpr levels even in the absence of infection [65]. Also, in a study of patients after neutropenic allogeneic bone marrow transplantation, serum CTpr levels were of little value in distinguishing infection from other complications [66].
In chemical pneumonitis due to inspiration of vomitus or to inhalation burn injury or inhalation of toxic fumes, there may be a sudden, marked increase in CTpr which is often proportional to the clinical severity of the insult [23, 67].
In pancreatitis associated with infected necrosis or caused by biliary obstruction, serum CTpr levels are higher than in the pancreatitis of alcoholism. Furthermore, in pancreatitis in general, high levels correlate with poor outcome [68, 69].
In burns there is a subgroup of patients who exhibit extremely high serum CTpr values in the first two days; these patients often have a rapidly fatal outcome. Patients who develop high levels later in the course often die of sepsis. Patients who never show high levels usually survive [22, 23, 70].
Heatstroke is usually accompanied by increases in serum CTpr, the level of which may correlate with the length of cooling time required for appropriate recovery [24].
Patients with systemic lupus erythematosus or autoimmune vasculitis do not have elevated levels of CTpr as assessed by the current commercial assay [20]. Whether an ultrasensitive CTpr assay would show elevated levels has not been determined.
Mild to moderate increases in CTpr may occur in various chronic inflammatory diseases in which neuroendocrine cell hyperplasia is a commonly associated factor (e.g. chronic obstructive pulmonary disease, chronic bronchitis, pulmonary tuberculosis, regional ileitis, ulcerative colitis). In evaluating the course of such illnesses it would be preferable to use an ultrasensitive CTpr assay. The lack of specificity of CTpr in surgical patients, patients with burns or patients with non-infectious inflammatory disorders could reveal the potential limitations of an ultrasensitive CTpr assay.
Circulating CTpr levels show increases in newborns which reverse spontaneously in the first week. If the correct reference ranges are applied, CTpr may nevertheless be used to diagnose microbial infections.
Patients with medullary thyroid cancer always have increased serum CTpr, as do most patients with small cell cancer of the lung or carcinoid tumour and, on occasion, patients with other neuroendocrine tumours such as pheochromocytoma [71, 72]. The usefulness of CTpr assays in evaluating the clinical course of such patients has not been studied.
* Many of the patient categories discussed in this table have what was initially defined a decade ago as "sepsis", i.e. the systemic inflammatory response syndrome associated with proven or presumptive bacterial infection. However, in patients with other conditions (e.g. pancreatitis, burns, chemical pneumonitis, trauma, surgery, severe illness due to viruses, fungi, or malarial parasites, etc.), translocation of bacteria and/or bacterial products across the intestinal wall may occur, producing a syndrome that is identical to sepsis and not uncommonly just as ominous in outcome. Furthermore, there is nothing to prevent patients with a translocation-induced sepsis-like syndrome from subsequently developing a secondary, exogenous, systemic bacterial infection. Note that in all instances, as is the case of many laboratory tests, a serum CTpr level must be evaluated with proper regard to the clinical and laboratory context of the patient studied.

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