CONTENTS

Airway receptors

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The conventional view of airway receptors is that there are four types (1).

Slowly adapting receptors (SARs). These are located in airway smooth muscle and are responsible for the Breuer-Hering inflation reflex; they play little part in cough although, when activated by a deep inflation of the lungs, the cough reflex is enhanced, partly by mechanical and partly by neural mechanisms (2).

Rapidly adapting receptors (RARs). These lie in and under the airway epithelium from larynx to bronchi and have fast-conducting myelinated (Aδ) nerve fibres. They show a range of properties, causing expiratory efforts from the larynx and trachea, cough from the larynx, trachea and large bronchi, and inspiratory efforts and hyperpnoea from the lungs (3,4). It is generally accepted that they are the main origin of cough, certainly with mechanical stimuli.

C-fibre receptors. These have slowly-conducting nonmyelinated nerve

fibres. They are found in all parts of the respiratory tract and lungs. They cause apnea and rapid shallow breathing but their role in cough is disputed. Selective stimuli to C-fibre receptors do not cause cough, while cough-inducing agents such as capsaicin may act by releasing neurokinins from the C-fibre receptors which in turn stimulate RARs (5).

Receptors related to neuroepithelial bodies (6). Their reflex actions are unknown.

In the last few years this traditional view has been transformed in several ways.

New receptors and subdivisions of the 'old' types have been identified. Thus there are Ad-nociceptors in the airway epithelium, with membrane properties and ganglionic pathways unlike those of RARs (7). The C-fibre receptors can be classified into subtypes (8). The possible roles of these new sensory receptor subtypes in cough have yet to be determined.

The identity of the pharmacological receptors on the terminal membranes of the nerves has been much studied, especially in relation to the tussive actions of capsaicin, acid solutions and touch (9); these studies point to the development of new peripherally-acting antitussive agents.

The 'plasticity' of the cough receptors and reflexes has been established, at peripheral, ganglionic and central nervous levels (10,11). These results have great relevance to the sensitisation of cough in inflammatory conditions such as asthma.

The central nervous pathways, including connections to the cerebral cortex, and interactions of the different afferent inputs have been delineated (12). This tells us more about how centrally-acting antitussive drugs work, and points to further developments here.

These exciting new advances have led to a surge in our understanding of neural mechanisms of cough, and in particular to its role and modification in disease, and to progress in antitussive therapy.

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The VR1 Receptor

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Capsaicin is a powerful stimulus which causes cough in experimental animals and in man. There is a large amount of evidence that the excitatory effect of capsaicin on sensory neurons is due to its ability to increase the open state of a channel previously defined as the 'capsaicin receptor'. This molecular entity has been cloned (Caterina et al., 1997) as a 426 amino acid protein, called vanilloid receptor-1 (VR1) and recognized as belonging to the transient receptor potential (TRP) family of ion channels.

The TRPV1, like many other ion channels possesses six putative transmembrane domains, with a proposed pore region between transmembrane domains five and six. All TRP are thought to have cytoplasmic N- and C- termini. Once activated by vanilloid molecules the TRPV1 allows the influx of cations (Ca^{2+} and Na^{+}). In terminals of primary sensory neurons these ionic events result in nerve terminal depolarization and the subsequent activation of action potentials that, by orthodromic conduction, initiate reflex responses, including cough. Ca^{2+}-influx into the nerve endings triggers the local release of neuropeptides, including calcitonin gene-related peptide (CGRP) and the tachykinins, substance P (SP) and neurokinin A (NKA). Activation of CGRP receptors and tachykinin (NK_1, NK_2 and NK_3) receptors on effector cells, particularly at the vascular levels, causes a series of inflammatory responses, collectively refereed to as neurogenic inflammation (Geppetti et al., 1996). TRPV1 is a thermosensor, activated by moderate noxious temperature between 42°C and 53°C (Caterina et al., 1997). Previous indication that the capsaicin-receptor could be stimulated by low extracellular pH (Bevan et al., 1994; Geppetti et al., 1991; Geppetti et al., 1996) was confirmed in the recombinant TRPV1 channel (Tominaga et al., 1998). Additional stimuli of the TRPV1 include elevated concentrations (in the μM range) of the endocannabionid, anandamide (Zygmunt et al., 1999), or the lipoxygenase metabolites of arachidonic acid, LTB_4 or 12-HPETE (Hwang et al., 2000). More recently, N-arachidonoyl-dopamine has been recognized as a TRPV1 stimulant, apparently more potent than anandamide (Harrison et al., 2003).

As with other TRP channels, and also for TRPV1 there are examples

that its expression can be upregulated or that its activity can be 'sensitized'. One clear indication of TRPV1 upregulation derives from the observation that TRPV1 protein expression in cell bodies of dorsal root ganglion (DRG) neurons is upregulated by inflammation occurring in their peripheral receptive areas. This upregulation is mediated by NGF and p38MAP kinase and results in an increased TRPV1 protein transportation to the peripheral endings of sensory neurons and in a parallel increase in heat hypersensitivity (Ji et al., 2002). Anandamide was shown to sensitize TRPV1 to other channel agonists. Anandamide also causes lowering of the threshold temperature to TRPV1 stimulation, an effect that was mediated by a protein kinase C (PKC)-e dependent pathway (Premkumar et al., 2000). More interestingly, activation of the bradykinin B_2 was found to result in TRPV1 sensitization by diverse intracellular mechanisms, including PKC-□e (Premkumar et al., 2000; Sugiura et al., 2002), displacement of phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) from TRPV1 binding (Chuang et al., 2001), and 12- and 5-lipoxygenase metabolites production (Carr et al., 2003; Shin et al., 2002). PKC-dependent TRPV1 sensitization seems to be promiscuously used by different stimuli, as in addition to anandamide, also heat and protons sensitize the channel by this enzymatic pathway (Vellani et al., 2001). Also cAMP-dependent PK (PKA) seems to be involved in TRPV1 sensitization (De Petrocellis et al., 2001), as capsaicin responses in sensory neurons exhibit a robust potentiation by PKA, as PKA reduces TRPV1 desensitization and directly phosphorylates TRPV1 (Bhave et al., 2002). The observation that prostaglandins may induce cough (Costello et al., 1985) and more relevantly, that one major adverse effect of angiotensin converting enzyme (ACE or kinase II) inhibitors is cough (Israili et al., 1992), suggests that bradykinin accumulation due to ACE blockade, either directly *via* a PKC-dependent pathway or, indirectly through prostanoid release, and a PKA-dependent pathway leads to TRPV1 sensitization and exaggeration of the cough response.

The identification of rather selective TRPV1 antagonists has been instrumental for the definition of the mechanism by which various agents provoke cough. Thus, the observation that anandamide-induced cough is blocked by both capsazepine and I-RTX (Jia et al., 2002) suggested that as in other experimental sets (Zygmunt et al., 1999) this lipid derivative produces its excitatory effects by TRPV1 gating. However, regarding anandamide it should be underlined its property as a cannabinoid receptor agonist, and that cannabinoid receptor activation inhibits sensory neuron stimulation (Tognetto et al., 2000) as well as cough responses (Patel et al., 2003). Two modes of sensory activation by protons were defined using extracellular recordings from single jugular or nodose vagal ganglion neurons that project their sensory fibers into the airways: a slowly inactivating mechanism, present in C-fibers but not in RAR-like fibers, that appears to be mediated by TRPV1; and a rapidly inactivating mechanism, independent of TRPV1, with characteristics similar to acid sensing ion channels (ASICs) present in both C-fibers and RAR-like fibers (Kollarik et al., 2002). From this studies it could be concluded that acid induced cough should be largely resistant to TRPV1 antagonists. In contrast with this hypothesis two independent studies (Lalloo et al., 1995) (Trevisani et al., submitted) showed that capsazepine almost abolished both capsaicin and citric acid induced cough in guinea pigs. The ability of protons to cause cough via TRPV1 activation is supported by the additional finding (Trevisani et al., submitted) that also I-RTX given by intraperitoneal route of administration or by aerosol abated citric acid-induced cough in guinea pigs. Both capsazepine and I-RTX did not affect hypertonic saline induced cough

(Trevisani et al., submitted).

Chronic cough is a condition sustained by a variety of different mechanisms. Pharmacological intervention to limit cough in the central nervous system has been proven successful, but adverse effects are not absent for current drugs acting at this level, and it is not difficult to predict that they can occur also for future similar drugs. Drugs acting at the peripheral level may have a more advantageous safety profile. However, given that fact that complex and pleiotropic stimuli initiate the tussive response, targeting a specific receptor or pathway at the peripheral level may not be an effective strategy. TRPV1 seems suited to be the target of different and clinically relevant cough stimuli. However, only clinical studies will answer the question whether TRPV1 antagonists are effective drugs to treat chronic cough in diseases such as postnasal drip, gastroesophageal reflux, asthma, chronic obstructive pulmonary disease, and other diseases.

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Central mechanisms subserving the cough reflex

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Previous studies have shown that the same medullary neuronal network involved in the generation of the eupneic pattern of breathing also participates in the production of the cough motor pattern[1,2,3] when triggered by appropriate afferent inputs.[4,5] It has been proposed that the excitability of the respiratory network during cough is additionally controlled by a 'gating' mechanism which is sensitive to antitussive drugs.[6] Recently, we have shown in the rabbit that microinjections of lignocaine or kainic acid into the Bötzinger complex (Böt. c.) region suppress spontaneous rhythmic expiratory activity and the cough reflex evoked by mechanical stimulation of the tracheobronchial tree.[7] In addition, we have provided evidence[8] that the excitatory drive to the expiratory neurons of the caudal ventral respiratory group (cVRG) is mediated by ionotropic glutamate receptors (mainly non-NMDA) during eupneic breathing, coughing and other respiratory reflexes. Respiratory neurons and interneurons located in different VRG subregions, including the pre-Bötzinger complex,[9] may have a permissive or even crucial role in the genesis of the cough reflex and be part of the proposed gating mechanism. However, several lines of evidence indicate that other neural structures may be elements of this mechanism.[2,10,11] Furthermore, it seems quite plausible that antitussive drugs may act at more than one central level. The main terminus of all cough-related afferents is the nucleus tractus solitarii (NTS). This medullary region, where non-homogeneous families of second-order neurons are located, appears to be the substrate of multiple and complex synaptic interactions;[1,2,5,12] it could be a site where modulatory actions of drugs on the cough reflex are exerted. In particular, rapidly adapting receptor (RAR) afferents terminate in the commissural nucleus and the caudal portion of the medial NTS.[1,2] We have obtained in the rabbit preliminary results showing that blockades of excitatory amino acid receptors within these regions lead to a reduction or suppression of the cough reflex, thus supporting the view that glutamate is the primary neurotransmitter at the synapses between RAR afferents and related second-order neurons.[5,12] We suggest that microinjections of selective agonists and antagonists of different neurotransmitters or neuromodulators may represent an useful tool in cough researches.

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Cough sounds

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Cough is often described without correlation with method to analize and measure cough sounds. To perform and validate an easier system for measure of cough, correlated with its frequency and acoustic patterns, we considered patients with asthma, chronic bronchitis, COLD and interstitial fibrosis. 5 cough events for each patient and 5 voluntary cough of 6 healthy controls were examined. Cough, via electrect microphone (ECM 144, Sony) was sent to an Audio Card multi Sound Tahiti, Pristine Audio Rec Card for acquisition and reproduction of sounds: Spectra Plus System, 3.16 (Poulsbo, WA, USA) was used for analysis by PCX4 100 MHz. Coughs in time (T) and Frequency (F) Domain (D), total duration, sonograms and spectra of the bursts were calculated. We found the parameters more useful to measure cough in TD, total duration, durations of the first and second burst; in FD: Central Frequency (CF) and percentile of F at 25%, 50%, 75% of the spectrum. We found in asthma: I Burst Duration 215 ms, Total duration 458 ms, Central Frequency 998 Hz; in chronic bronchitis: I Burst Duration 312 ms, Total duration 615 ms, Central Frequency 1398 Hz; in COLD: I Burst Duration 410 ms, Total duration 798 ms, Central Frequency 1808 Hz; in interstitial fibrosis: I Burst Duration 195 ms, Total duration 401 ms, Central Frequency 719 Hz (Cfr tab 1). For I Burst, Total Duration and Central Frequency there are significant ($p<0.001$) differences between ILD mean values and COLD and CB; significant ($p<0.005$) between COLD and CB and poor between CB and BA. For all parameters there are overlapped data to signify and difficulty in differentiating the cough of BA Vs CB. The cough patterns are more evident in the pure pathologies and more repetitive in the same patients. The "error rate" is about 8-14%.
It is possible also to describe the cough sounds with noninvasive cough monitoring system based on a portable phonometer. It is a new approach to the problem by detecting cough in free field without any physical connection to the patient. The equipment is based on: 1. An Integrating Sound Level Meter which consents the sounds analysis, real time frequency and Fast Fourier Trasform analysis (System 824 SLM/RTA, Larson Davis, UT, USA); 2. A Software N&V (Spectra s.r.l. ML I),

32 bit for Windows for calculation, analysis in time-frequency domain, graphical representation by sonograms and automatic identification of events, working with PC-Autotrsf., Audio File for simultaneous acquisition of audio associated to the events. The detection of cough was made by asking the subjects to cough voluntarily and spontaneously, to loudly speech, sighing and snoring, to identify the event of cough and validate the system. In all subjects studied the count of cough events presenting as sonograms exactly corresponds to the cough sounds emitted and counted by two observers. In all cases, by audio file, the identification of a single cough event, has been possible random or in a series and the differentiation from similar impulsive events due to voluntary simulation. The automatic counting, based on fixed time-frequency parameters in the 99.9% of cases identify the cough sounds.

The Clinical Value Cough Provocation Tests

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Cough is a significant clinical problem[1], however, one of the obstacles to the understanding of cough is the lack of a simple means of assessing it objectively. While it is feasible to record cough events using a variety of recording techniques none have proven applicable for wide scale use. On the other hand subjective measures such as questionnaires are of value in understanding the impact on an individual and describing it[2], but lack the sensitivity to be used in small studies. Could cough challenge testing provide the objective measure that is needed?

In theory cough reflex testing like bronchoprovocation should be of value in epidemiology studies. Unfortunately no true epidemiology study has used cough reflex testing as a variable there is, however, data from small studies, which point to its possible value. Broadly speaking the studies show that in the non-coughing population there is little variability in the cough reflex sensitivity[3]. There is some evidence that children are more sensitive than adults[4] and females more than males[5] but this may well be an artefact of dosing due to their smaller airways. The cough reflex has been studied in a number of different patient groups with respiratory diseases with and without cough. Patients with stable disease without cough have a normal reflex[3], however, if the disease is associated with dry cough then an increased sensitivity of the reflex has been observed[3]. On the other hand the patients who had stable productive cough were likely to have a normal cough reflex. However, there is evidence that the reflex sensitivity increases during exacerbations[3].

Cough provocation testing could have two roles in clinical practice. First, a use in making a diagnosis and second a use in monitoring disease or treatment progress. The data available would support limited if any utility in diagnosis other than showing that an abnormal response was present would indicate organic disease. Cough reflex testing is more likely to find a role in disease assessment and progression monitoring. A clear example is in patients with stroke[6] where the observation that an absent response to challenge was a better predictor of lung infection than an abnormal voluntary cough test shows promising use for the provocation test. Prospective studies in common cold[7] and angiotensin converting enzyme inhibitor cough[8] show that people with a normal reflex developed an increased response that normalised on resolution of the cough. Patients have, also, been followed during treatment in a cough clinic[9]. Those who responded to therapy not only showed a symptomatic improvement but also showed a parallel decrease in the sensitivity of their reflex. However, in those patients who did not respond to therapy the reflex abnormality remained. These studies indicate that the test could be

abnormality remained. These studies indicate that the test could be used to monitor the disease progress.

In hypothesis testing and drug development cough provocation testing is mandatory as there is no other practical method for studying mechanisms, which may increase or decrease cough. In addition drugs that have been shown to clinically alter cough i.e. opiates[10], local anaesthetics[11] and demulcents[12] have been shown to reduce the sensitivity of the reflex assessed by a number of challenges. Where as drugs with no proven anti-tussive activity in the clinic also failed to show activity in cough challenge testing.

I have review its clinical utility and would support its use in epidemiology and hypothesis testing but to date there is no strong evidence yet to suggest its use in routine clinical practice.

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Il ruolo dell'otorinolaringoiatra nella valutazione della tosse cronica dell'adulto

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La progressiva affermazione nella pratica clinica del protocollo di indagine anatomo-funzionale proposto da Irwin alla fine degli anni settanta per lo studio dei pazienti portatori di tosse cronica ad eziologia sconosciuta, ha definito in modo chiaro il ruolo dei diversi specialisti che concorrono alla corretta valutazione del «Tratto Respiratorio Integrato» inteso nel suo complesso (vie aeree superiori, medie ed inferiori). Lo specialista ORL è pertanto chiamato ad un impegno di primaria responsabilità per cui, nella valutazione clinica del paziente, è assolutamente necessaria una specifica attenzione a segni e sintomi che possono essere potenzialmente rapportabili al sintomo tosse. Va sottolineato come all'esame specialistico convenzionale (rinoscopia anteriore, orofaringoscopia, laringoscopia e rinofaringoscopia indiretta) vada associata, specialmente nelle situazioni di difficoltà ispettiva o di dubbio, una valutazione fibroendoscopica praticabile sia con ottiche rigide che flessibili. Questo esame, in genere ben tollerato dai pazienti consente, infatti, di condurre un'ispezione molto più accurata dell'intero distretto otorinolaringoiatrico, ed in particolare, di alcune zone critiche difficilmente esplorabili con l'esame convenzionale come la parte posteriore e la parete laterale delle fosse nasali, la rinofaringe e la regione commisurale anteriore della laringe. Inoltre attraverso le registrazioni e l'archiviazione computerizzata delle immagini o dei filmati, tale indagine consente di effettuare accurate valutazioni dei dettagli patologici ed altrettanto accurate valutazioni del risultato terapeutico nel follow-up del paziente. Quando l'esame rinofibroscopico mette in evidenza alterazioni compatibili con una potenziale patologia sinusale allora diverrà indicato lo studio del massiccio facciale attraverso almeno una tecnica di imaging (TC oRMN). Tale impostazione diagnostica, pur non trascurando tutte le possibili cause di tosse cronica di pertinenza ORL (infettive, allergiche, neoplastiche,…), ha lo scopo di individuare se possibile le 2 condizioni che si sono dimostrate più frequentemente essere causa di tale quadro clinico. Esse sono rispettivamente il cosiddetto «post nasal drip» (PND) o gocciolamento retronasale e la malattia da reflusso gastroesofageo (GERD) caratterizzata da sintomi atipici. Il PND che risulta in assoluto la causa più frequente di tosse cronica idiopatica nell'adulto, con una variabilità compresa tra il 41 e 67% nelle differenti casistiche, è caratterizzato da una sintomatologia rappresentata da tosse non produttiva, non parossistica, prevalentemente mattutina o dopo un cambiamento posturale (passaggio dal clino all'ortostatismo o viceversa), sensazione di secrezioni presenti in sede retronasale e faringea, rinorrea e necessità di schiarirsi frequentemente la gola (clearing throat) e/o di soffiarsi il naso.

L'obiettività oro-rino-faringoscopica evidenzia la presenza e il ristagno di secrezioni mucoidi o mucopurulente, la mucosa faringea può presentare il tipico aspetto ad "acciottolato" («cobblestone mucosa» o faringite cronica granulosa) per l'ipertrofia dei follicoli

linfatici sottomucosi diffusi nell'ambito delle pareti faringee; può essere infine presente una laringite posteriore caratterizzata da edema e\o lieve ridondanza, iperplasia ed iperemia della mucosa interaritenoidea.
L'esame radiologico del cranio o la TAC del massiccio facciale rivelano una opacizzazione delle cavità parasinusali con possibile presenza di livelli idroaerei ed ispessimento del rivestimento mucoso.
Possono essere inoltre considerati criteri di orientamento diagnostico sia la risposta ad una terapia farmacologica specifica orientata in base ai criteri clinici e radiologici sopraccitati (antibiotici, antistaminici, cortisonici), che l'esclusione di altre possibili cause mediante l'utilizzo del protocollo diagnostico proposto da Irwin.
Anche se l'ipotesi di una patologia con dignità nosologica autonoma (PND) in grado di correlare in un unico quadro anatomo-fisiopatologico all'interno del TRI la maggior parte delle affezioni flogistiche potenzialmente connessa alla tosse cronica è sicuramente suggestiva, rimane comunque da chiarire quale sia la sua reale incidenza in pazienti con tosse cronica sia quanti, tra i soggetti con diagnosi di PND, non riconoscano in realtà una genesi multifattoriale della tosse («mixed diagnosis patients»). Tali considerazioni critiche trovano la loro giustificazione in primo luogo in relazione al fatto che il quadro obiettivo faringolaringeo proprio del PND è assolutamente aspecifico: per esempio l'aspetto ad acciottolato della mucosa faringea e l'eventuale presenza di secrezioni siero-mucoidi caratterizzano molte rinofaringiti croniche spesso asintomatiche; inoltre il quadro dell'edema interaritenoideo o più in generale la cosiddetta «laringite posteriore» rappresenta anche un segno clinico del reflusso gastroesofageo a presentazione atipica, quindi soprattutto nelle forme sfumate, è soggetto ad una notevole variabilità di interpretazione. In secondo luogo è molto importante sottolineare come nella maggioranza delle riniti vasomotorie e delle sinusiti croniche, anche in quelle con importante opacizzazione delle cavità paranasali documentata radiologicamente, è assai più frequente che la tosse risulti del tutto assente.
In sintesi, sebbene sia giustificato considerare il PND un'entità clinica a sé stante, potenzialmente causa di tosse, è necessario che la diagnosi preveda un oculato esame del paziente ed una attenta e critica valutazione dei dati laboratoristici e strumentali.
Per ciò che concerne il GERD a presentazione atipica esso risulta essere causa singola o in associazione con PND o asma in una percentuale variabile dal 15 al 30 %. Ancora una volta l'otorinolaringoiatra ha semplicemente il compito di sollevare, in base alla valutazione clinica faringolaringoscopica, il sospetto di responsabilità di tale patologia nella genesi della tosse. Anche in questa circostanza i sintomi e i segni clinici sono del tutto aspecifici, tuttavia la corretta integrazione tra segni obiettivi ed anamnesi del paziente (episodi di pirosi gastrica o retrosternale, precedente rilievo di ernia iatale …) permettono di dare giustificazione ad una richiesta di consulenza gastroenterologica.
In conclusione a fronte di un paziente con tosse cronica idiopatica la valutazione ORL, pur non differendo in modo sostanziale dall'esame specialistico convenzionale, deve saper individuare sintomi e segni clinici spesso frequenti e del tutto aspecifici che, proprio per tale motivo, sfuggono ad una adeguata valorizzazione sul piano clinico, ma che in questi pazienti rappresentano la spia di una associazione tra la tosse ed il PND o la malattia da reflusso gastro-esofageo (GERD). È altrettanto importante che lo specialista, pur sulla base di reperti aspecifici, sappia indicare le ulteriori indagini atte a confermare in modo attendibile la presenza di una delle suddette associazioni. Solo da tale atteggiamento deriverà sia il corretto inquadramento eziologico

del paziente che la migliore prospettiva di successo terapeutico.

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Diagnostic strategy in patients with GOR related chronic cough

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It has been already well established that typical reflux symptoms, like heartburn and regurgitation, are reported as main complaints by no more than two thirds of patients with GE reflux and physicians are increasingly aware that GERD has many atypical or extraesophageal manifestations. Chest pain may represent a major clinical problem for a fraction of patients but it is not properly an extraesophageal manifestation since it can origin from esophageal motility disorders. Thus, when we speak about the extraesophageal manifestations of GERD we must consider mainly the oro-pharyngeal or pneumologic manifestations. These are represented by many symptoms and signs, going from very mild, like hoarseness, to very severe disease, like cancer. Pneumologists and otolaryngologists have probably emphasized the role of GE reflux but there is no doubt that, at least for the major manifestations like asthma, cough and laryngitis, reflux seems to account for a relevant proportion of cases. In patients with chronic cough, reflux is considered the cause in as many as 20% of cases and in this respect it is the third leading cause after asthma and nasal problems. There are basically two mechanisms by which reflux may elicit oropharyngeal or pulmonary symptoms. One is a proximal extension of the refluxed materials (direct action) and the other is a vagal reflex arising from the distal esophagus (indirect action). Both mechanisms may simultaneously be involved and the crucial point is represented by the presence of acid into the esophageal lumen. The aim of the diagnostic strategy in these patients with extraesophageal symptoms is, basically, the demonstration of reflux disease and for the achievement of this goal we have four main tools: clinical features, endoscopy, 24-h pH-metry and a trial of aggressive acid suppression (PPI test). However, if we want to optimise our strategy in order to reduce the number of investigations we should base the choice of the work-up on the test sensitivity in this particular setting. Clinical features do not help us very much since literature data have clearly shown that esophageal symptoms are scarcely reported by patients with reflux-related asthma, cough or laryngitis and probably more than 50% of these patients deny having esophageal complaints. Thus,

at least in half of the cases, we must go on with our investigations. Endoscopy may be a very useful tool provided that we find esophageal lesions since the presence of esophagitis allows a positive diagnosis of GERD without any further investigation. Unfortunately, if we look at the prevalence of esophagitis in patients with different manifestations of reflux disease we must realize that in the largest published studies esophagitis is found in approximately 25-40% of patients with asthma and only in 10-30% of those with oro-pharyngeal symptoms. Therefore the diagnostic sensitivity of endoscopy is very low in these patients and it should not be considered as a first level investigation. Also a finding of a posterior laryngitis during a laryngoscopy has been proposed for the diagnosis of extraesophageal GERD but the sensitivity of this endoscopic feature is quite low, about 50%, and therefore shouldn't be used for the diagnosis of reflux laryngitis. Of course, 24-h esophageal pH-metry represents the gold standard for the measurement of GE reflux. In this kind of patients it may be performed with a dual probe, that is with a simultaneous assessment of acid reflux at two different esophageal sites, 5 cm above the LES and immediately below the crycopharyngeal sphincter. However the evaluation of reflux with a proximal probe seems to have some limitations since the assessment of reflux at a proximal site has a low reproducibility. Thus, also in patients with extraesophageal symptoms, a classic distal pH-metry should be performed. Esophageal pH-metry has an acceptable sensitivity, which is higher in patients with typical reflux symptoms and particularly in those with esophagitis. Its sensitivity in patients with extraesophageal presentations is quite variable depending mostly on the patient selection. In general the more recent data, obtained in patients with asthma or chronic cough, show a sensitivity ranging from 50 to 80%. The finding of a pathologic acid reflux represents an important step-up toward a diagnosis of extraesophageal GERD but 24-h pH-metry gives also the opportunity of proving the existence of a causal link between symptoms and reflux, provided that the patient had his symptoms during the recording period and that the Symptom Index (S.I.) evaluated during pH-metry is higher than 50%. These conditions are rarely found in patients with extraesophageal GERD and the S.I. evaluation doesn't help very much from a practical point of view. But we have another important tool for establishing the origin of symptoms in our patients. An empirical trial with PPI has been recently proposed for the diagnosis of GERD in patients with different clinical presentations. The principle of the test is that an aggressive acid suppression may dramatically improve the symptoms of the patient if they are caused by esophageal acid exposure. The results obtained in different patient groups have shown that the test has in general a good sensitivity and that in patients with extraesophageal presentations we need a higher daily dosage and a prolonged period of administration. The PPI empirical trial is an attractive, simple and cost-effective diagnostic test and its use may be particularly helpful in patient groups with a low prevalence of pathologic reflux. The test may be used instead of pH-metry or after a negative pH-metry in order to find out the patients with the so-called hypersensitive esophagus. In patients with extraesophageal manifestations, and particularly in those with associated esophageal symptoms, the PPI trial (double daily dose for at least 4 weeks) may well represent the first step of our diagnostic work-up.

La tosse nell'asma

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La tosse può essere l'unico sintomo nei soggetti adulti asmatici. Di solito non è produttiva, può associarsi ad un'espettorazione mucoide e le sue manifestazioni di variabilità, periodicità e pattern sono gli aspetti che la rendono caratteristica dell'asma. Ad esempio, alcuni asmatici sono costretti a svegliarsi per la tosse nelle prime ore del mattino, mentre altri presentano una tosse sempre più manifesta durante la giornata, che conferisce un tipico aspetto a denti di sega al time-course della misurazione diurna del PEF. In uno studio sulla qualità della vita, condotto con una survey postale, i 272 pazienti asmatici moderatamente severi seguiti in day hospital denunciavano, in modo del tutto inaspettato, la tosse diurna e la mancanza di respiro come sintomi di maggiore impatto rispetto al respiro sibilante o i disturbi del sonno.[1] L'allergia e l'asma sono caratterizzate da alterazioni fisiopatologiche che hanno alla base l'infiammazione eosinofila e che sono determinanti nella comparsa di tosse nei pazienti che ne sono affetti. All'infiltrazione cellulare ed al conseguente rilascio di mediatori chimici fanno seguito altri stimoli che interessano tre gruppi di recettori nervosi sensoriali presenti nelle vie aeree: i recettori delle fibre C, i recettori a rapido adattamento, i recettori delta-nocicettivi di tipo A. Le fibre C mediano il riflesso assonico tra infiammazione neurogena e broncocostrizione, e

regolano la secrezione mucosa e l'iperemia secondaria al rilascio di neuropeptidi. Questi aspetti, ben documentati negli animali di laboratorio, non sono tuttavia supportati nell'uomo da studi con buone evidenze scientifiche. L'attivazione dei recettori innesca un arco riflesso che interessa il midollo allungato ed il sistema nervoso centrale, con un complesso gioco di interazioni dovuto a neuro trasmettitori chimici. I riflessi che ne derivano comportano broncocostrizione, secrezione e vasodilatazione mucosa. Il riflesso della tosse dipende dall'interazione di tre circuiti riflessi di base: a livello periferico, dei gangli e del sistema nervoso centrale.[2] La prevalenza della tosse nell'asma è difficile da stabilire anche se essa è un sintomo molto frequente, soprattutto nei bambini asmatici. Nel caso di tosse cronica di questi ultimi l'infiammazione eosinofila è rara e la frequenza della tosse è simile tra asmatici e controlli in età scolare. Vi sono alcuni aspetti che possono indurre confusione e la vera tosse asmatica può essere definita come una varietà di sintomi che vanno dall'asma classica, di cui la tosse è un sintomo cronico ed occasionale, alla tosse "variante asma" o alla bronchite eosinofila, di cui la tosse è l'unica manifestazione sintomatologica. In ogni caso la tosse spinge il paziente a recarsi dal medico per una visita più di ogni altro sintomo [3], probabilmente perché incide in misura significativa sulla sua qualità della vita. Una tosse presente da alcune settimane, associata a fischi, sibili espiratori ed un radiogramma del torace normale, viene trattata con cortisonici e broncodilatatori per via inalatoria. La risposta favorevole al trattamento, testimoniata dal miglioramento clinico-funzionale, non significa necessariamente che si sia davanti ad un asmatico, perché i farmaci potrebbero avere sedato la tosse grazie al loro meccanismo antinfiammatorio o alla loro attività sulla clearance muco-ciliare. Tuttavia, la tosse può essere anche la sola ed unica manifestazione dell'asma. Le differenze tra asma classica e tosse "variante asma" non sono particolarmente significative e, nonostante l'infiammazione eosinofila sia comune ad entrambe, riguardano sostanzialmente la presenza nella tosse "variante asma" di un numero inferiore di eosinofili nel sangue periferico, una minore presenza eosinofila nell'espettorato ed una minore reattività bronchiale al test di provocazione aspecifica con metacolina. Tali differenze non sono rilevanti sul piano statistico, stando ai risultati di uno studio comparativo tra le due forme, peraltro basato su gruppi di pazienti scarsi per numerosità. [4] La diagnosi di asma dev'essere sempre confermata da un test di provocazione bronchiale con metacolina, che evidenzia la presenza di iperreattività bronchiale. In questo caso, la risposta alla terapia, la presenza di iperreattività bronchiale e l'andamento cronico della malattia sono i punti chiave sui quali si fonda la diagnosi di asma bronchiale. Un risultato negativo del test alla metacolina esclude (tranne in caso di esposizione professionale al toluene diisocianato) che la causa di tosse cronica possa essere l'asma; infatti, il test ha un valore predittivo negativo del 100 %, mentre il suo valore predittivo positivo è variabile tra il 60 e l'88 %. La diagnosi di tosse "variante asma" comporta uno schema terapeutico simile a quello dell'asma, ma il mancato miglioramento della sintomatologia dopo la somministrazione di steroidi inalatori dovrebbe orientare verso una falsa positività del test di provocazione bronchiale aspecifica. Al contrario, il miglioramento clinico che si manifesti dopo la somministrazione di corticosteroidi sistemici non autorizza la diagnosi di asma bronchiale in assenza del risultato di un test alla metacolina, perché diverse situazioni cliniche causate dall'infiammazione, come ad esempio la rinite allergica o la bronchite eosinofila, rispondono con successo al trattamento cortisonico. [5] La bronchite eosinofila si associa a tosse cronica nel 13 % dei casi ed è caratterizzata dalla presenza di eosinofili e cellule metacromatiche nell'espettorato simili a quelle dell'asma, da cui però differisce per la mancata associazione ad iperreattività bronchiale. La bronchite eosinofila può essere associata o meno all'asma, manifestandosi anche in caso di tosse cronica senz'asma o in qualche sporadico caso di BPCO, patologia in cui la classica risposta infiammatoria è di tipo neutrofilo e non eosinofilo. La diagnosi di bronchite eosinofila può essere esclusa quando gli eosinofili, nell'espettorato indotto, sono meno del 3 % rispetto alle cellule non squamose.[6] Un esaltato riflesso della tosse, misurato anche con altri test da stimolo, quali ad esempio la capsaicina, l'acido citrico o la nebbia ultrasonica, contribuisce alla presenza di tosse nell'asma e non è vero che la tosse sia dovuta alla necessità di rimuovere secrezioni dalle vie aeree. L'accresciuta reattività tussigena alla capsaicina, sostenuta anch'essa da meccanismi infiammatori può essere ulteriormente esaltata nel caso di prolungata esposizione allergenica durante la stagione pollinica, nei pazienti asmatici allergici. Ciò farebbe pensare ad una modificata responsività neurogenica secondaria all'infiammazione allergica; in altre parole, alla possibilità di un rapporto causa-effetto tra infiammazione delle basse o alte vie respiratorie e meccanismi neurogeni, che assumono significatività sul piano clinico.[7] L'assenza di correlazione tra risposta alla capsaicina e limitazione al flusso, misurata con il FEV-1, conferma che i meccanismi che stanno alla base di ostruzione delle vie aeree sono diversi da quelli che causano la tosse, almeno per i pazienti con BPCO. [8] A differenza dell'asma classica, nella tosse "variante asma" non c'è evidenza di ostruzione bronchiale; il sintomo principale è infatti la tosse

non c'è evidenza di ostruzione bronchiale; il sintomo principale è infatti la tosse secca, dei cui aspetti di fisiopatologia si sa pochissimo. È stata descritta un'ipersensibilità dei recettori della tosse ed un aumento della densità dei recettori nell'epitelio delle vie aeree. [9] La sensibilità dei recettori della tosse alla capsaicina, aumentata nell'asma, non è associata né all'iperreattività bronchiale [10] né all'infiammazione eosinofila delle vie aeree nei pazienti con asma allergica i cui sintomi principali sono dispnea e fischi, ma non tosse.[11] Questi aspetti rendono il test alla capsaicina di limitata utilità per il management e la diagnosi differenziale dell'asma.[10] Il declino funzionale polmonare nella tosse "variante asma" non è particolarmente diverso, rispetto alla tosse degli atopici o della popolazione normale, così come l'assunzione di corticosteroidi inalatori non ha alcun effetto sulla pendenza della retta che descrive il declino della funzione respiratoria, ma può svolgere un'azione di prevenzione sulla trasformazione della tosse "variante asma" in asma classica. Infatti, la tosse "variante asma", a differenza della tosse atopica, è considerata una manifestazione che precorre l'asma tipica. [12] [13] È stata ipotizzata, con qualche fondato sospetto, un'associazione tra tosse e polluzione atmosferica legata al traffico, anche se non si possono trarre conclusioni certe su un possibile sviluppo di asma.[14] I bambini che abitano distretti metropolitani ad elevato tasso di inquinamento ambientale presentano odds ratio maggiori per tosse (1.74) ed espettorazione frequente (1.87), espettorazione cronica (1.84) ed asma (1.98), diagnosticata dal proprio medico di famiglia. Hanno inoltre valori funzionali respiratori inferiori rispetto ai propri coetanei che vivono in distretti a minore tasso di inquinamento atmosferico. [15] La malattia da reflusso gastro-esofageo è un'altra delle cause di tosse cronica e può dar luogo ad una reazione asmatica. I meccanismi del reflusso comportano sia una micro che una macro-aspirazione, uno stimolo chimico laringeo ed un riflesso mediato dal nervo vago. Ma nell'asma da reflusso si ha evidenza anche della presenza di infiammazione neurogena. Il trattamento medico o chirurgico del reflusso gastro-esofageo consente di ottenere un miglioramento nel 70 % dei casi della sintomatologia dell'asma, compresa la tosse. La chirurgia del reflusso gastro-esofageo sembra avere migliori effetti sulla tosse che sull'asma. [16] Un trattamento empirico di tre mesi con omeprazolo, 20 mg al dì, è il miglior metodo per diagnosticare un'asma da reflusso ed anche quello dotato di migliore rapporto costo-efficacia. Nei soggetti non-responder è opportuno un controllo del pH esofageo nelle 24 ore. [17] [18]

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Eosinophilic Bronchitis

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Clinical features and diagnosis

Gibson et al.,[1] first identified eosinophilic bronchitis without asthma as a cause of chronic cough in 1989. Eosinophilic bronchitis is defined as a chronic cough in subjects with no symptoms or objective evidence of variable airflow obstruction, normal airway hyperresponsiveness (provocative concentration of methacholine producing a 20% decrease in FEV_1 [PC_{20}] > 16mg/ml) and a sputum eosinophilia.[2] A similar corticosteroid responsive cough syndrome has been reported by Fujimura *et al* and has been given the diagnostic label 'atopic cough'.[3] Whether eosinophilic bronchitis and atopic cough represent distinct clinical entities is unclear.[4] As with other causes of cough, details of nature and timing of the cough are of limited help in establishing a diagnosis of eosinophilic bronchitis but in our experience it is a predominantly dry cough with small amounts of tenacious sputum in the mornings that typically responds to inhaled

corticosteroids. Making a positive diagnosis of eosinophilic bronchitis therefore requires assessment of lower airway inflammation after other causes of cough have been excluded by clinical, radiological and physiological assessment. We use a >3% sputum eosinophil count as indicative of eosinophilic bronchitis as this is well outside our normal range (<1.9%) and this level of sputum eosinophilia has been associated with a corticosteroid response in COPD and asthma.[5,6] Induced sputum is a safe, valid and repeatable measure of airway inflammation.[7] Exhaled nitric oxide, another non-invasive marker of airway inflammation has been proposed as a simpler alternative to induced sputum tests. Exhaled nitric oxide levels are usually higher in eosinophilic bronchitis[8,9] but its role in the diagnosis of eosinophilic bronchitis has not been evaluated. One small report found that eosinophilic bronchitis was the cause of chronic cough in 10% of cases.[10] We have recently reported a 2-year prospective study of chronic cough.[2] Ninety-one patients with chronic cough were identified among 856 referrals. A diagnosis leading to a successful treatment was reached in 85 (93%) of the cases. Eosinophilic bronchitis was amongst the commonest causes of chronic cough and was identified in 12 (13.2%) patients.

Treatment

Anti-inflammatory treatment with inhaled corticosteroids is the mainstay therapy for eosinophilic bronchitis. Patients improve symptomatically and have a significant fall in their sputum eosinophil count following inhaled corticosteroids.[11,12] In one study capsaicin cough sensitivity, which was moderately increased before treatment,[12] improved towards normal following treatment with budesonide (400μg inhaled twice daily) and there was a significant positive correlation between the treatment induced change in cough sensitivity and sputum eosinophil count. There is no data currently available to guide which inhaled corticosteroid should be used for eosinophilic bronchitis, at which dose and for how long. In our experience, improvement begins in 1-2 weeks. Very occasionally oral corticosteroids are required to control symptoms and eosinophilic inflammation. It remains unclear whether therapy for eosinophilic bronchitis should be discontinued when symptoms resolve. The role of other potential therapies such as antihistamines and anti-leukotrienes needs to be explored.[13]

Pathogenesis of eosinophilic bronchitis

One of the main interests is why an apparently similar pattern of airway inflammation is associated with different functional abnormalities in eosinophilic bronchitis and asthma. Conceivably this might reflect functionally important differences in site, state of activation or regulation of inflammatory response. Both conditions share several immunopathological features including a sputum,[9] bronchoalveolar lavage[9,13] and biopsy eosinophilia, increased Th2 cytokine expression [14] basement membrane thickening[9,15] in bronchial biopsy and increased sputum supernatant concentrations of cysteinyl-leukotrienes and eosinophilic cationic protein.[16] Interestingly, histamine and PGD_2 concentrations were only increased in eosinophilic bronchitis suggesting that activation of mast cells in superficial airway structures is a particular feature of this condition and raises the possibility that localisation of activated mast cells might differ in asthma and eosinophilic bronchitis. In support of this, we have recently found that mast cell numbers in airway smooth muscle are increased in asthma, but not in eosinophilic bronchitis.[15] Furthermore airway smooth muscle mast cell numbers inversely correlated with airway hyperresponsiveness. Thus a key factor determining the different functional association of airway inflammation in eosinophilic bronchitis and asthma might be the microlocalisation of mast cells with a predominant airway smooth muscle infiltration resulting in airway hyperresponsiveness and variable airflow obstruction, and an epithelial infiltration producing bronchitis and cough. The specific role of the mast cell in the bronchial epithelium of patients with eosinophilic bronchitis and its interactions with cough sensory afferents needs further study.

Natural history of eosinophilic bronchitis

The natural history of eosinophilic bronchitis is unclear. A ten year follow up evaluation of the twelve patients from the original reports of eosinophilic bronchitis suggests that this condition is generally benign and self-limiting.[17] However, our experience is somewhat different. We have follow-up data of more than one year from 32 patients

We have follow up data of more than one year from 32 patients identified between 1996-2003. Three (9%) of our patients developed asthma with typical symptoms and airway hyperresponsiveness. Twenty-one (66%) had persistent symptoms and or ongoing airway inflammation. Only one patient with eosinophilic bronchitis had complete resolution of symptoms and had no sputum eosinophilia whilst not on corticosteroid therapy. Five (16%) developed fixed airflow obstruction, although the decline in FEV_1 in the whole group of patients with eosinophilic bronchitis was not greater than in normal controls. Several studies have observed that 30-40% of patients with COPD without a history of asthma and with no bronchodilator reversibility have sputum evidence of an airway eosinophilia.[5,18] Our observation provides one possible explanation for the presence of eosinophilic airway inflammation in some patients with COPD without apparent pre-existing asthma in that eosinophilic bronchitis may in some circumstances be a prelude to COPD. Our findings are similar to that reported for atopic cough where there was no increased decline in lung function[19] and progression to asthma was rare.[20]

Conclusions

Eosinophilic bronchitis is a common and treatable cause of chronic cough. The airway inflammation is similar to that seen in asthma although eosinophilic bronchitis is associated with quite different abnormalities of airway function. Recent findings support that these differences might be related to the site of mast cell infiltration of the airways. Future studies need to define clearly the natural history of eosinophilic bronchitis and investigate the effects of other therapies.

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Measurement of cough. Subjective versus objective measurements

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Cough is a symptom associated with a wide range of diseases of the airway, from acute upper respiratory tract viral infection to asthma and gastro-oesophageal reflux. The fundamental trigger for cough is airway inflammation and a sensitisation or hyper-reactivity of airway sensory nerves that mediate cough. The inflammation of the airway is the trigger for cough and it is possible to measure the concentrations of markers of inflammation in the airway such as histamine or the presence of eosinophils, but it is the act of coughing and the severity of cough that disturbs the patient and it is cough that causes the patient to present for treatment.

A major problem in studying cough and developing new treatments for cough is that there is no generally accepted measure of cough. In conditions such as hypertension the blood pressure can be easily and accurately measured. This makes it relatively easy to grade the severity of the disease and to determine the efficacy of any interventions that are designed to lower blood pressure. Studies on

cough treatments rely on changes in cough counts and cough frequency as measures of the efficacy of any treatment but it is often difficult to decide what constitutes a single cough as bouts of cough give complex cough sounds. Similarly one must decide if a high intensity cough is an equivalent or greater problem to the patient than a low intensity cough. Measurement of cough is further complicated by sounds such as throat clearing and vocalisation that can be confused with cough when data is gathered electronically and analysed by computer. In an attempt to overcome some of the limitations of cough counts we have developed a method of measuring the total amount of cough sound by means of a sound level meter [1]. However, this method cannot distinguish between cough and other sounds and therefore is only of use in a laboratory study. Methods of ambulatory cough recording have been developed but these methods are often cumbersome and usually require the recording of both cough sounds and lower respiratory muscle electromyography in order to separate cough sounds from other sounds such as speech [2].

Cough is under voluntary control and patients can readily cough on command or suppress cough as and when required [3, 4]. The voluntary control of cough adds an extra complication to the measurement of cough as patients may inhibit cough in response to any form of treatment that they believe will influence cough. The voluntary control of cough may be responsible for the large placebo effect associated with cough treatments [5].

Objective measures of cough are useful in the assessment of cough medicines but it is also necessary to demonstrate that the patient can perceive some benefit of the treatment by use of subjective scores or quality of life measures. A statistically significant reduction in cough counts is of no clinical benefit if the patient does not 'feel' better. Subjective scores may use categorical scales of 'not present, mild, moderate, severe' or a 100mm visual analogue scale with the ends labelled from 'no cough' to 'most severe cough'. In some studies there is only a poor correlation between the objective measures of cough and the subjective scores and this demonstrates that subjective and objective measurements may measure different aspects of cough [6]. The subjective scores may take into consideration other factors such as the impact on behaviour and the level of embarrassment associated with cough.

Since cough causes physical and pyschosocial complications it has the potential to lead to a decrease in health-related quality of life (HRQoL) [7]. Prospective studies have shown that cough can adversely affect HRQoL [7]. A study using patients with chronic cough, acute cough and cough associated with smoking has shown that a health related quality of life score may be a reliable and useful tool for assessing the efficacy of cough therapies [8].

At present there is no consensus on whether objective, subjective or quality of life measures provide the best measure of efficacy of any new therapy. This lack of agreement in standardising the measurement of cough makes it very difficult to conduct clinical trials on cough medicines as there is uncertainty about which measure of cough to use as an outcome measure in any clinical trial.

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Quality of Life

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Chronic cough produces a highly significant deleterious effect on the qualify of life of both the coughers and their immediate relatives. This effect is obvious when taking the history. Patients have missed work and school, and been barred from social activities, either activity or passively by the patient's own reluctance to attend such functions. The history may reveal physical effects of chronic cough such as syncope and incontinence. The formal structuring of these quality of life issues was initiated by Cynthia French, who has demonstrated both the reproducibility of the cough quality of life instrument but also its sensitivity in terms of being able to quantify patient response.

Unfortunately quality of life instruments are difficult to transpose across cultures. In Leicester (UK) Surinder Birring and colleagues have produced a validated qualify of life instrument applicable to the UK. Again, this instrument has been shown to be reproducible and sensitive.

What can be achieved by the use of quality of life measures? The first achievement of these questionnaires has been to demonstrate the degree of disability suffered by patients with chronic cough. Many regard this as a little more than a nuisance whereas in fact studies by both French and Birring have demonstrated greater detriment. Secondly, these instruments can be used to determine treatment efficacy. This has always been a problem in cough studies because of the episodic and variable nature of the symptom. Finally, such quality of life instruments may be used via the Internet. In an exciting development we have established an Internet information resource for patients who complete the quality of life questionnaire and submit them to our server, which marks and grades the answers to the questionnaires and provides patients with advice as to treatment and

life style modification.

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Risultati dello studio AIST

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L'incidenza del sintomo tosse varia nella popolazione generale dal 5% al 40% in base alle caratteristiche ambientali, all'età della popolazione, alla stagione e all'abitudine al fumo. In Italia la tosse costituisce, in ordine di frequenza, la terza causa che induce il paziente a consultare il proprio medico di medicina generale, mentre in ambito specialistico, la tosse persistente ad eziologia sconosciuta rappresenta il 10-35% della normale pratica ambulatoriale.
Da tutti gli studi finora condotti emerge come le patologie che più frequentemente risultano responsabili di una tosse cronica siano: il gocciolamento retro-nasale, l'asma bronchiale, il reflusso gastroesofageo. Queste tre affezioni costituiscono, da sole o in associazione, circa l'80% di tutte le cause di tosse persistente.
Lo studio AIST, che ha coinvolto 12 Centri Nazionali*, si è posto come obiettivi:

- valutare le relazioni esistenti tra sintomatologia di presentazione e caratteristiche eziologiche della tosse;
- stimare la prevalenza delle diverse forme eziologiche della tosse;
- osservare l'evoluzione della sintomatologia in relazione alla terapia seguita.

Il nostro studio, di tipo osservazionale e longitudinale si è svolto nel periodo Gennaio 2002 - Settembre 2003 su 216 pazienti con tosse cronica da almeno 3 settimane ed è stato seguito da un periodo di arruolamento sequenziale e consecutivo di 6 mesi ed una serie di follow-up periodici ad 1,6 e 12 mesi. La ricerca è stata condotta seguendo un preciso iter diagnostico-terapeutico basato su un Protocollo multidisciplinare preparato da Pneumologi, Gastroenterologi ed Otorini.
Un primo Report statistico, relativo all'analisi dei dati basali e dopo 1 mese (elaborato da QUBIsoft), conferma quanto riportato in letteratura relativamente all'incidenza dell'eziologia e ai risultati diagnostico-terapeutici. I dati finali riguardanti i risultati a 6 e 12 mesi verranno presentati al Convegno Nazionale AIST nel febbraio 2004.

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The use of diagnostic protocols for cough

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The evaluation and successful treatment of chronic cough is a difficult clinical challenge. Some patients may need only baseline investigations and short courses of treatment although others require a more involved approach. Important questions have arisen as to the complexity and cost effectiveness of existing cough protocols[1]. Guidelines for the evaluation and treatment of cough have been produced although there is no agreement as to the optimum strategy to adopt[2,3]. Review of specialist cough clinic experience identifies considerable variance in the diagnostic approach and reported treatment outcomes[4,5,6,7]. Current strategic options range from a 'test all, then treat' approach to a more empirical 'treat first, then review' approach. Cost effectiveness analysis suggests the 'test all' approach as most expensive but with shortest treatment duration while the 'treat first' approach is cheapest but with longest treatment duration[1]. The challenge therefore appears to be balance of cost with time to treatment success.

At present, any diagnostic protocol for evaluating patients with chronic cough should continue to appreciate the three most common aetiologies, which may operate singly or simultaneously. It should ensure both correct interpretation of diagnostic tests and the timely inclusion of empirical trials of therapy, which should be of adequate dose and duration.

The move towards a fuller understanding of the pathogenesis of cough, new technological advances in quantifying cough and the availability of novel therapeutic options, is likely to alter diagnostic protocols for cough in the future.

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Effect of Stroke Location on the Laryngeal Cough Reflex and Pneumonia Risk

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To evaluate the efficacy of testing the laryngeal cough reflex (LCR) in identifying pneumonia risk in acute stroke patients. A prospective study of 818 consecutive acute stroke patients in an acute rehabilitation hospital setting using the reflex cough test (RCT) to assist in clinical patient management. The binary end point for the study outcome is the development of pneumonia.

Brainstem (p-value <.007) and cerebral strokes (p-value <.005) correlated with the RCT results and pneumonia outcome. Of the 818 patients utilizing the RCT, 35 (4.3%) developed pneumonia. Of the 736 (90%) patients who had a normal RCT, 26 (3.5%) developed pneumonia, and of the 82 (10%) patients with an abnormal RCT, 9 (11%) developed pneumonia, despite preventive interventions (p-value <.005). The statistical power analysis for this comparison was 0.80. There were no serious adverse events of the RCT.

With a normal RCT the airway is reflexively protected, and it is safe to initiate a bedside swallow evaluation. An abnormal RCT indicates risk of a neurologically unprotected airway, an increased incidence of pneumonia, and the need for alternate feeding strategies and preventive measures. The RCT acts as a reflex hammer for assessing the LCR and the vagal cough system. Despite stroke location, many patients may demonstrate a condition we call "brainstem shock." Brainstem shock may be defined as a global neurological condition involving a transient or permanent impairment of one or more of the following vital functions: respiratory drive, reticular activating system, or the LCR.

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Complicanze della tosse

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La tosse è un atto complesso, altamente coordinato, che dà luogo alla espulsione rapida dell'aria alveolare a velocità molto elevata; ha lo scopo di ripulire le vie aeree da gas irritanti, polveri, fumo, eccesso di muco, residui cellulari o pus.
Quando stimoli chimici o fisici attivano i recettori della tosse, il processo si sviluppa con tre differenti fasi: fase inspiratoria, di compressione e fase espulsiva. La fase inspiratoria della tosse comincia con una inspirazione profonda che determina un incremento dei volumi polmonari ed un aumento della pressione di ritorno elastico. Durante la fase compressiva la glottide si chiude e i muscoli espiratori cominciano a contrarsi con incremento della pressione pleurica, addominale ed alveolare sino ed oltre 100 mmHg. Nella fase espulsiva la glottide si apre bruscamente e l'alto gradiente pressorio genera un flusso espiratorio che raggiunge il massimo in 30-50 millisecondi con un flusso alla bocca fino a 12 litri al secondo. L'aria espulsa attraverso la trachea, fortemente ristretta per la compressione dinamica, agisce staccando il materiale estraneo o le secrezioni spingendole alla bocca.
In questo alternarsi di contrazione dei muscoli inspiratori ed espiratori e di rapide ed ampie oscillazioni pressorie possono verificarsi eventi patologici che coinvolgono numerosi organi ed apparati.
La pressione intratoracica molto alta causa la compressione delle vene cave intratoraciche, la diminuzione spiccata del ritorno venoso al cuore e l'aumento brusco della pressione venosa generale. Nello stesso tempo il repentino aumento della pressione intratoracica e intraddominale viene trasmesso attraverso i fori intervertebrali al liquido cerebro spinale con la possibilità che si determini una ischemia cerebrale temporanea, specie se la portata cardiaca è simultaneamente diminuita con comparsa di stordimento, sincope, emorragie nelle piccole vene della faccia e del collo.
La frattura delle coste può essere spiegata dalla deformazione operata dalla parossistica contrazione muscolare che supera le capacità elastiche delle stesse, nella zona più vulnerabile, il terzo medio. Le fratture possono evidenziarsi in ogni costa, anche se le più comunemente coinvolte sono quelle comprese tra il quinto e il decimo paio. Alla base delle rare lacerazioni diaframmatiche durante tosse è la mancata coordinazione dei diversi muscoli espiratori.
Nei polmoni integri durante la tosse non si assiste a rottura delle pareti alveolari in quanto la contrazione dei muscoli espiratori determina l'incremento della pressione intrapleurica consensualmente a quello della pressione alveolare senza alterazione della pressione transmurale. La situazione cambia se si considera un polmone con alterazione della architettura alveolare, come nel caso di enfisema, in cui l'applicazione delle intense variazioni pressorie della tosse può

sul l'applicazione delle intense variazioni pressorie della tosse può causare pneumomediastino o pneumotorace che ulteriormente aggravano il quadro clinico di base.

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Chronic Cough in Children

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All children cough, but most children are normal. Cough is difficult to assess, with only the poorest correlation between history and objective measurements [1,2]. The physician faced with a child with a chronic and relatively non-specific symptom such as cough first needs to decide into which of five categories to place the child:

1. Normal child (the diagnosis which requires the most skill and experience)
2. A child with a serious illness such as cystic fibrosis, tuberculosis etc (rare, but essential to get right)
3. A child with non-serious, but treatable causes of cough and wheeze, for example gastro-oesophageal reflux or postnasal drip.
4. A child with an asthma syndrome
5. Overestimation of symptoms for psychological or other reasons by either or both of child or family.

Initial assessment is with a careful history and physical examination. It should be noted that the likelihood of a child having a serious condition depends on the setting; in a community context, isolated cough rarely betokens anything serious, but in a tertiary level hospital, selection ensures that many more coughers have a serious underlying cause.

Specific categories of cough

"Nursery school syndrome" Many particular first time parents do not

realize the frequency with which viral infections occur in toddlers when they first go to a child care facility (about every three weeks on average). These children have chronic infective rhinitis, cough vigorously and are well, although they may keep themselves and their families up at night. Reassurance should be given; cough linctuses are useless; and I suspect many seek the help of complementary therapists.

Post-bronchiolitic cough and other symptoms Respiratory syncytial virus (RSV) bronchiolitis is a common scourge of infancy. Prolonged cough and wheeze are common after the acute illness. Inhaled steroids are valueless in these post bronchiolitic syndromes [3-5]. Although a therapeutic trial with bronchodilators or inhaled steroids is often attempted, especially in atopic children, it usually does nor work. Parents should be reassured that the symptoms will improve [6,7] in the long term, and over-treatment should be avoided.

Coughing with viral colds All children cough with colds. Excessive coughing even without wheeze may be a variant of asthma (below). Such symptoms solely at the time of viral colds under age one year is not miniature adult asthma. A number of physiological and prospective studies have shown that this phenomenon is not due to an inflammatory airway phenotype, but due to reduction in baseline airway calibre, almost certainly on a developmental basis. The first important principle is that lung function may be influenced by the intra-uterine environment before birth. Two studies using tidal breathing indices of lung function [8,9], and one using the squeeze technique to produce partial flow volume curves [10] have clearly demonstrated that infants have abnormal lung function very soon after birth; risk factors include a maternal history of atopy, maternal smoking and (interestingly and quite unexplained) maternal hypertension during the pregnancy. The second principle is that infants who cough and wheeze with colds have evidence of airway obstruction before the first wheezing episode. This has been confirmed by three large prospective studies [11-13] using different lung function measurements in different populations wheeze with viral colds have abnormal lung function before their wheezing episode. Thus current best evidence is that those who cough and/or wheeze with viral colds do so because of adverse effects on airway calibre prior to birth, probably in the second half of pregnancy. The third principle is that coughing and/or wheezing with viral colds may not be associated with either BHR or airway inflammation. Two studies showed no increase in BHR in children who wheezed with viral colds [14,15]. A study in which blind bronchoalveolar lavage was carried out in children at the time of elective surgery showed that children who wheeze with viral colds did not have inflamed airways, unlike the atopic asthmatics [16]. Long-term, children who wheeze with viral colds have normal lung function whether or not they are prescribed inhaled steroids [17]. Children who wheeze with viral colds in general respond poorly to inhaled steroids [18], but a therapeutic trial may be justified (see above), but they should be discontinued if they do not work. There is no evidence that intermittent high dose inhaled steroids commenced at the onset of a viral cold are of any value. Most paediatricians (including myself) would be more inclined to use prophylactic inhaled steroids early in atopic children, even though many will outgrow their symptoms by the start of the school years [19]. There is clearly a huge need for a simple test to identify those infants with wheeze and cough who are at high risk for ongoing symptoms and long term impairment of lung function.

Does true cough variant asthma exist? Cough is undoubtedly a common symptom of asthma; can it be the only symptom, and if so, how commonly? The answer will be different, depending on the setting in which the question is posed. There is no doubt that large epidemiological studies show that in a community setting, where by definition the vast majority of children are well, isolated cough is rarely due to asthma and rarely responds to asthma medications [20,21]. There is also no doubt that isolated cough may frequently be over-diagnosed as asthma [22]. Chronic non-specific cough frequently improves with time and without treatment [22,23]. However, in a specialist clinic, where a highly selected group of children are seen, children who cough in response to typical asthma triggers, and improve when treated with asthma medications are not uncommonly seen. My diagnostic criteria are:

1. Abnormally increased cough, with no evidence of any non-asthma diagnosis
2. Clear-cut response to a therapeutic trial of asthma medications (see below)
3. Relapse on stopping medications with second response to recommencing them

Many children with chronic cough in fact have only a non-specific problem, and have been shown on bronchoscopic and blind lavage studies to have no evidence of eosinophilic airway inflammation [24]. Follow up studies show that most will get better over 1-2 years. Others however will show evidence of deterioration of BHR over time, wheeze, and develop the picture of classical asthma [25]. If coughing is troublesome and the precautions outlined above are followed, then there is little to be lost attempting a brief therapeutic trial. The only danger is that ineffectual and potentially harmful medication may be continued long term unless a trial off therapy is rigorous. In older children who can perform lung function, there is no justification for a therapeutic trial without making every attempt to document variable airflow obstruction.

Chronic paroxysmal cough The importance of cough as a symptom of asthma has been so drummed into us, that there is a real danger that every cough of any duration is treated as asthma. Fairly regularly I see children with paroxysmal cough, sometimes with vomiting or even whooping, of several weeks duration. Invariably they have had a failed trial of inhaled steroids. Some are undoubtedly due to pertussis, others probably a result of infection with mycoplasma or viruses. Typically, the child is well between paroxysms, but the paroxysms when they come are extremely distressing. The family should be reassured and commiserated with, and all treatment stopped. Some of these children may be left with a propensity to cough excessively with future viral colds. I have never seen a formal description of this syndrome, but it undoubtedly exists, and is not asthma.

"Honk" cough This is absolutely characteristic - once heard, never forgotten. It is a loud, stereotyped, barking noise, quite unlike any organic cough. It is exceedingly irritating to all around, and continues unabated until the child falls asleep, quite unlike any cough signifying underlying disease. Unless the key question "What happens when the child is fast asleep?" is asked, a series of negative investigations and escalating and useless therapeutic trials performed, with no benefit. Once the diagnosis is appreciated, symptoms may respond to relaxation and control of breathing exercises performed by a physiotherapist. If this approach fails, then psychological intervention

is required. Not infrequently, quite profound disturbance is discovered.

A few clinical catches Cystic fibrosis characteristically causes failure to thrive as well as chronic cough. However, around 15% are pancreatic sufficient at diagnosis, and thus thrive - this frequently results in diagnostic delay. It should be noted that delayed diagnosis is not rare - 10-15% may not be diagnosed until adult life, usually presenting with respiratory rather than gastrointestinal symptoms.
Primary ciliary dyskinesia (PCD) is also frequently not considered, even in a child with dextrocardia and neonatal onset of symptoms, until bronchiectasis has developed. Typically, the child has rhinitis from birth (often fatuously diagnosed as being born with a cold!) which continues unabated. A chronic wet cough is common. This condition is not rare (estimated 1 in 15,000 live births), and failure of diagnosis can result in considerable iatrogenic upper airway morbidity, as well as progression to bronchiectasis [26]. Once the diagnosis has been made, however, the best evidence is that progression of respiratory disease can be halted, and upper airway morbidity avoided [27,28].

Recent Research in Paediatric Cough Monitoring In order to try to overcome the problems of assessing cough, we have studied a modified monitor in children with cystic fibrosis and asthma. We confirmed the poor correlation between cough assessment by children and objective outcome in cystic fibrosis [29]; recent data [Li et al, Thorax, in press] has shown that cough is increased in apparently well controlled asthmatics; that it is predominantly during the day not the night; and that it correlates not with lung function, but an index of airway inflammation, exhaled nitric oxide. There is clearly a need for more research in the objective assessment of cough in children, and its relationship with inflammation and airway disease.

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La tosse nel paziente pediatrico: approccio diagnostico

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La tosse è uno dei sintomi più frequenti in pediatria ed uno dei principali motivi di consultazione per il pediatra (1).
A tutte le età infezioni virali delle vie aeree superiori (URI) sono responsabili di episodi di *tosse acuta*, cioè che duri non più di 1-2 settimane, non produttiva o scarsamente produttiva (2). Come regola generale, un bambino affetto da tosse iniziata da meno di tre settimane, scatenata da una URI, in assenza di altri sintomi e con un esame obiettivo negativo, non necessita di accertamenti.
Si parla di *tosse cronica* o, meglio, *persistente* nei casi in cui la durata del sintomo superi le 3 (4-6 secondo alcuni) settimane. Una tosse che dura più di tre settimane è inusuale per una semplice URI, mentre può essere un segno di varie malattie (3-5). Dato il suo ruolo protettivo, la tosse, specialmente quella persistente, non dovrebbe mai essere trattata con farmaci "soppressivi" senza prima aver cercato di stabilirne la causa (o le cause).
Sebbene siano numerose le possibili cause di tosse persistente in età pediatrica, la stragrande maggioranza delle volte la diagnosi rientra in una "triade eziopatogenetica" che comprende il gocciolamento nasale posteriore (Postnasal Drip, PND), l'asma bronchiale e la malattia da reflusso gastroesofageo (Gastroesophageal Reflux Disease, GERD). Tuttavia la diagnosi *eziologica*, l'unica che permette di arrivare alla risoluzione del sintomo nella maggioranza dei casi, non è sempre agevole.

Ci sono evidenze a favore di un approccio "razionale e sistematico" del sintomo tosse, mediante l'utilizzo di "protocolli o linee guida" rispetto ad un approccio "variabile e non sistematico": i tempi per giungere alla diagnosi si riducono da molti mesi a poche settimane (5). Sono stati suggeriti vari protocolli diagnostici per la tosse, tutti più o meno validi, alcuni più adatti all'età pediatrica (6,7); ma, in tutti i casi, non si può prescindere dalla raccolta di un'accurata anamnesi (età del bambino, tipo di esordio, epoca d'inizio del sintomo, caratteristiche della tosse, familiarità), dall'esecuzione di un esame clinico completo e di alcuni esami chimico-clinici e strumentali di primo livello.
Quando non si rinviene una patologia precisa, deve essere presa in considerazione la tosse psicogena o tic della tosse, che è sempre una diagnosi di esclusione. La tosse psicogena tipicamente interessa soprattutto bambini di età superiore ai 7 anni ed il sesso femminile con una frequenza doppia rispetto ai maschi; è una tosse secca, a tonalità alta, scompare di notte e peggiora con l'ansia e lo stress; gli esami clinici sono tutti negativi ed i sedativi della tosse risultano inefficaci.

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Cough and allergy

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Asthma and rhinitis are the most common clinical manifestations of atopy, and a strong relationship exists between these two conditions and cough.

Although most episodes of cough in children are not asthma, there is now little doubt that asthmatic children can even present with cough as the initial symptom. So much so that the international guidelines on management of asthma in children define asthma as "recurrent wheezing and/or cough in a context in which asthma is likely..." [1]. Furthermore, parents may not recognize wheezing [2]

likely…" [1]. Furthermore, parents may not recognize wheezing [2]. The relationship between asthma and cough is indeed very strong. In a study in which tracheal sounds were continuously recorded in 60 asthmatic children and 30 controls [3], cough was present in asthmatic children in 92% of recording time during asthma exacerbations and 7% of recording time during remission, versus 6% of recording time in non-asthmatic children. In an unselected group of children hospitalised because of an asthma episode, almost 50% of parents reported that their children had cough usually or always during asthma exacerbations [4]. Furthermore, in asthmatic children who presented with cough Chang et al. have shown a temporary increase of cough receptor sensitivity during asthma exacerbations [4]. However, several studies have shown the lack of correlation between asthma severity and cough severity [4,5].

The relationship between atopy, asthma, bronchial hyperreactivity (BHR) and cough is quite complex. A study comparing 60 preschool children with isolated cough with 60 asthmatic children and 60 healthy controls [6] found that children with isolated cough were significantly more atopic (63%) than controls (10%), but asthmatic children were significantly more atopic (80)% than children with isolated cough, suggesting that children with isolated cough are a heterogeneous population. Atopy is related to BHR [7], but its presence is not constant. In a longitudinal study [8] 5% of children had negative skin prick tests 3.5 years later, while 13% of children developed positive tests. Furthermore, while atopy tended to increase with age, BHR tended to decrease [8]. While there is no doubt that asthmatic children are more likely to have BHR than asymptomatic children [9], BHR is not always synonymous of asthma [9,10]. BHR was reported in children with cystic fibrosis and allergic rhinitis, as well as in 7-33% of asymptomatic children [9-11]. On the other hand, BHR is absent in 6-33% of children with recurrent wheezing [9,11]. Some studies have shown an association between cough and BHR [7,12]. The proportion of children with cough having BHR is 14-39% [7] and, after adjusting for wheezing, no significant association remained between cough and BHR [13]. Studies trying to verify whether BHR in children with isolated cough is associated with subsequent asthma have provided discordant results.

Allergic rhinitis (AR) is also an important cause of chronic cough [14]. Besides cough, children with chronic AR typically have hypernasal speech, fatigue, decreased appetite. Poor growth, resulting from chronic infections and inflammatory conditions such as sinusitis, may also be present. Cough in AR and sinusitis results from postnasal drip and irritation of the larynx.

Several studies have tried to investigate the relationship between sensitisation to single allergens and clinical symptoms. In general, after adjusting for all other allergens, sensitisation to house dust mite and cat dander has been reported to be associated with wheezing and asthma, while sensitisation to grass pollen was found to be associated with AR. It has also been suggested that pollen allergens can cause lower respiratory symptoms after being fragmented. Capsaicin cough sensitivity was found to be increased in allergic asthmatic patients during prolonged allergen exposure as during the birch pollen season [15]. Skin prick test sensitivity to alternaria was also reported to be associated with asthma and wheezing in the regions where the levels of alternaria spores are high. In a recent study on 849 infants with an asthmatic sibling, persistent mould exposure significantly increased the risk of wheezing and persistent cough in the first year of life [16]. A recent intervention study on primary prevention of asthma and atopy [17] shows that strict allergen avoidance in infancy in high risk children reduces the development of allergic sensitisation to house dust mite and suggests that this may reduce the prevalence of wheezing and nocturnal cough at age 8.

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GOR - related cough in children: the surgical option

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BACKGROUND
Respiratory pathology in patients affected by gastroesophageal reflux is a well known situation and its characteristics involve a wide clinical variety. In the patients affected by gastroesophageal reflux resistant to medical treatment (postural therapy, diet and pharmacological therapy) the gastric fundoplication, nowadays laparoscopically performed, has achieved the disappearance of gastroesophageal reflux and consequently the resolution of respiratory symptoms in the most part of cases in which gastroesophageal reflux and respiratory disease were linked. Moreover we have to report that the development of mini-invasive surgery has made patients more able to bear with this kind of surgical treatment obtaining a significant reduction of bed stay.

METHODS

From 1970 till today at the Pediatric Surgical Department of Bologna 216 fundoplications were performed.
From May 1996 to September 2003 in 109 patients we performed laparoscopic fundoplication. Age ranged from 4/12 to 17 yrs (average 6 yrs 3/12). Indication for surgery included also gastroesophageal reflux associated with recurrent upper airway infections, acute bronchitis, asthmatic attacks, ab ingestis pneumonia, resistant to medical therapy. Preoperative evaluation included barium swallow, upper gastrointestinal endoscopic examination and 24-hour pH-metry. Patients who undergo surgical treatment are placed on the table on back with spread legs to allow the access to the first operator and in anti-Trendelemburg position. After positioning a nasogastric tube, telescope is inserted, under direct vision, in a supraumbilical 10 mm primary trocar. CO_2 pneumoperitoneum is created with maximal insufflation pressure of 6 to 8 mm Hg. A special parietal retractor inserted below the xiphoid process allows such a reduced pressure holding on the round ligament. Once inserted 4 more operative trocars, we proceed to the isolation of abdominal esophagus and perform the fundoplication. In relation to the exigencies, gastric placation may be made with a complete 360° degree wrap of the gastric fundus around the esophagus according to Nissen ("floppy Nissen"), with an anterior wrap according to Dor or Thal or with a posterior one according to Toupet. Nasogastric tube is taken away on the first postoperative day and feeding is started on the second one. The mean length of postoperative hospital stay is of 3-4 days.

RESULTS

In the check-up made after one, three and six months, the patients have no gastroesophageal reflux linked symptom and a significant improvement in their respiratory function mainly in neurologically impaired patients with a story of previous ab ingestis pneumonia.

CONCLUSIONS

Patients affected by gastroesophageal reflux resistant to medical therapy and associated with recurrent and reactive airway disease, show improvement in their respiratory status following fundoplication

show improvement in their respiratory status following fundoplication with, in the most part of cases, quick weaning off of the medical oral management. These results suggest that fundoplication is a safe and effective treatment for a complete resolution of both gastric and respiratory diseases linked to gastroesophageal reflux.

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Cough in patients with congenital central hypoventilation syndrome

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Congenital lack of central chemosensibility is the main functional deficit of a rare disorder, the congenital central hypoventilation syndrome (CCHS). CCHS is defined as failure of the chemical (autonomic) control of breathing causing central alveolar hypoventilation in the absence of pulmonary, cardiac, or neuromuscular disorders or of patent brainstem lesions (1, 2). Patients have absent or markedly reduced ventilatory responses to sustained hypercapnia and hypoxia (3, 4). Hypoventilation is predominant in non-rapid-eye-movement sleep, during which breathing is primarily under chemical control. Pathophysiological mechanisms of CCHS are unknown, but failure of the central integration of chemosensory inputs is proposed as the putative defect (5). Central defects in CCHS appear a widespread autonomic system disorder and patients may also present with ocular anomalies (6), oesophageal dysmotility (7), abnormal control of heart rate (8) and blood pressure. About 20% of CCHS patients also have Hirschsprung disease, a familial and sporadic disorder characterised by deficient development of the enteric nervous system. Rare CCHS patients suffer from neural crest derived-tumours (6). A genetic basis for CCHS is supported by lines of evidence. Familial cases have been reported in monozygotes twins, female siblings, and male-female half-siblings.

Little is known regarding cough in CCHS patients. Parental reports seem to suggest that coughing during airway infection is weak in these patients; furthermore, some lines of evidence seem to suggest that patients with CCHS lack a cough response following inhalation of a tussigenic agent (10). This study will analyse the sensory and motor component of coughing in CCHS patients. Furthermore, since cough is elicited by stimulation of receptors also implicated in the control of breathing pattern, we will also evaluate the ventilatory adjustments evoked by inhalation of tussigenic concentrations of ultrasonically nebulised distilled water (fog).

At this stage, we have studied 1 15 yr-old patient with CCHS and 4 control subjects aged 6-12 yr. Cough was induced by inhalation of progressively increasing fog concentrations and cough threshold was defined as the lowest concentration (in ml/min) capable of eliciting cough during two distinct fog challenges separated by a 30 min interval (11). Cough was indexed in terms of cough peak flow and

peak integrated electromyographic activity of the abdominal muscles (IEMGp). The pattern of breathing was recorded by means of a calibrated inductive plethysmograph (Respitrace). In all participants, respiratory sensations possibly provoked by fog inhalation were assessed by means of a specifically designed questionnaire.
In control subjects, fog inhalation consistently induced coughing; the threshold fog concentration ranged from 0.4 to 3.26 ml/min. In most subjects (3 out of 4), the appearance of cough was preceded by significant increases in minute ventilation ($P<0.05$) that were accounted for by selective increases in tidal volume. Mean inspiratory flow rate also significantly increased ($P<0.05$). The appearance of cough was accompanied by the perception of "tickling in the throat" or "tickling in the chest". In addition, all subjects reported the sensation of an "urge to cough" that occurred within a few seconds prior to cough onset. In the CCHS patient, fog inhalation up to a level corresponding to the maximum nebuliser output (4.45 ml/min) failed to induce a cough response. Furthermore, fog inhalation caused no detectable change in the pattern of breathing, nor was accompanied by any respiratory symptom.
These preliminary results indicate that fog inhalation causes no respiratory response in the CCHS patient. If confirmed in larger number of patients, the results would point to an impairment of the peripheral or central mechanisms involved in the mediation of cough in CCHS patients.

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