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特 別 講 演

腸管内正常細菌叢と化学療法剤

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人は出生すると，間もなく微生物の汚染をうけて皮膚，気道，消化管などの粘膜でいろいろな微生物が増殖してくる。誕生後の数日間の糞便からは *E. coli*, Enterococci, Lactobacilli, Clostridia, Staphylococci などが出現し，この菌数は $10^{9\sim10}$/g である。その後，離乳期までは特徴ある腸内細菌叢を形成する。すなわち，母乳栄養児ではビフィズス菌が腸内細菌叢の殆どを占めているが，混合栄養児のそれでは母乳栄養児と同様にビフィズス菌が最優勢菌として出現することが多いが，ビフィズス菌が検出されない乳児もみられる。さらに特徴的なことは，混合栄養児では母乳栄養児と異なり，成人の糞便と同様に *E. coli*, Enterococci などの好気性菌の菌数が多いことである。成人の腸内細菌叢を構成している菌種，菌数は宿主により若干異なるものの，ほぼ一定の構成を示している。細菌数は $10^{10\sim11}$/g である。菌種は *Bacteroides*, Eubacteria, Peptostreptococci, Bifidobacteria, Clostridia などの嫌気性菌で糞便内細菌叢の最優勢を占め，*E. coli*, Streptococci, Lactobacilli, *Veillonella*, Staphylococci などは $10^{5\sim7}$/g 程度しか検出されない。このような腸内細菌叢は健康な固体ではかなり安定しているが，宿主の生理，食物，薬剤，気候，感染，ストレス，腸内細菌の相互作用，年齢などにより変動する。

腸内細菌叢は宿主にたいして有用性と有害性の相反した二面性の働きをしている。有用性ではビタミン合成，消化・吸収，感染防御，免疫刺激など，有害性では腸内腐敗，細菌毒素，発癌物質産生などにより下痢・便秘，肝臓障害，動脈硬化，高血圧，癌，自己免疫病，免疫抑制などの誘因が挙げられている。一方，腸内細菌叢の構成菌には compromized host の内因性感染症の原因菌となりうる菌種が多い。

何等かの理由により腸内細菌叢の構成が撹乱された場合，下痢や出血傾向の高まることがあることは衆知のところである。

ところで，抗菌剤性偽膜性腸炎，下痢症の原因菌として *Clostridium difficile* が重要視されている。事実，抗菌剤性偽膜性腸炎の下痢便から *C. difficile* およびその毒素が 95～100% に検出される。しかし，抗菌剤性下痢症の下痢便から *C. difficile* および毒素の検出率は 20～30% である。したがって，内視鏡検査で偽膜の認められない抗菌剤性下痢症では *C. difficile* 以外の原因によることが多い。その原因菌としては，いずれも毒素産生性の *Clostridium perfringens* A, C, E 型菌，*Clostridium spiroforme*, *Clostridium sordellii* などが注目されてきた。これらの細菌は人や動物の腸管内に少数常在しており，抗菌剤投与により腸内細菌叢が質的，量的に乱れた宿主腸管内で異常増殖して毒素を産生して下痢を起こすものと考える。これらの細菌は病院環境内からも検出されることが多く，抗菌剤性偽膜性腸炎，下痢症は病院内感染症としても考慮されるべきものと考える。

私は，腸内細菌叢と化学療法剤との関係について，主として下痢症を中心に，発症機序を毒素，腸内細菌叢と化学療法剤とのかかわりについて述べたい。

招 請 講 演

Bacterial Adherence in Respiratory Tract Infections

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Introduction

The mucosal surface of the respiratory tract represents the initial defense barrier protecting the host against infection with a variety of microorganisms. Invading organisms must either pass quickly through the barrier, gaining access to deeper tissues and ultimately, the blood stream, or establish residence on the mucosal surface. Failure to accomplish one of these results in removal of the organisms by physical mechanisms, princi-

pally swallowing. Rapid penetration of the mucosal barrier is uncommon and the great majority of pathogenic organisms, both viral and bacterial, initiate their unique pathogenetic sequence of events by establishing residence in the upper respiratory tract. Persistence of a microorganism at a particular site is termed "colonization". The distinction between colonization and actual infection is often difficult. Most authorities require evidence of either a host response or tissue injury to identify infection. Thus, colonization indicates the persistence of a given microorganism in the absence of a host response or injury to the host. Presumably, most pathogenic organisms establish a state of colonization for at least some period of time before causing clinically recognizable infections. If adherence to host tissues is important at all in the pathogenesis of respiratory tract infections, it would most likely play a role in promoting colonization.

Selective adherence, or the adherence of only certain microbes to the cells lining a certain region of the body, could form the basis for the maintenance of a "normal bacterial flora"[1]. The factors responsible for the presence of only certain bacterial species in the upper respiratory tracts of humans and lower animals have been the subject of much speculation for many years. Recent evidence suggests that bacterial adherence may be the major determinant of the normal flora and provides a plausible framework in which other, time-honored mechanisms may also be operative. One of the latter might be bacterial antagonism in which one species of bacteria inhibits the growth of another ; despite experimental support for this mechanism extending back to Pasteur, proof that bacterial antagonism is an important factor in the regulation of the respiratory tract flora has been circumstantial at best.

Mechanisms of Adherence

Unfortunately for purposes of clarity, bacteria appear to adhere to mammalian cells through a variety of different mechanisms. Not only do the mechanisms differ among bacterial species, but multiple adherence mechanisms may be important for a single species. These factors complicate study of the adherence process and greatly complicate understanding of the significance of a given observation. Further, both bacterial and host factors influence the adherence process so that mechanisms which might be important in adherence to one type of cell may not be important for another. Finally, it should be remembered that study of the adherence process is usually conducted *in vitro* and the conditions under which the assay is performed may differ markedly from those which exist *in vivo* so that it is difficult to draw firm conclusions from this type of observation.

Bacteria generally bind to cells via surface appendages known as pili or fimbriae. The site of binding is called the "adhesin" and the cell binding site a "receptor". It appears that many bacteria-cell interactions involve highly specific binding reactions[2]. Adhesins are often proteins while cell receptors most often are carbohydrate-containing components of membrane glycolipids or glycoproteins. Adherence can be blocked by altering either. Incubation of bacteria with antibody against pili, purified pilus proteins, or highly purified adhesin protein blocks subsequent adherence to cell surfaces[3,4]. Conversely, preincubation of the bacteria with analogs of the receptor carbohydrate also blocks subsequent adherence. Mannose has shown to be one of the important ligand molecules for the adherence of many Enterobacteriaceae, including *Escherichia coli*[5]. However, fucose, galactose, fructose and other sugars may be involved in the adherence of the same or other bacterial species. Differing carbohydrate specificities may account for the predilection of organisms to infect only certain tissues, as well as serving to confuse investigators. For example, binding of *E. coli* to both buccal and bladder epithelial cells is inhibited in the presence of mannose but the propensity of this organism to colonize and infect renal tissue appears to be much more strongly related to the ability of some strains to adhere to galactose-containing membrane proteins[6].

Streptococci and probably staphylococci bind poorly to the surface of buccal epithelial cells but adhere readily to fibronectin, a protein normally present on these cells[7]. Thus, in this situation, coloniza-

tion appears to result from the presence of a protein adsorbed from the local milieu, since fibronectin is not known to be produced by these epithelial cells. Removal of cell-surface fibronectin causes a decrease in the adherence of streptococci. Interestingly, loss of fibronectin and decreased adherence of streptococci is accompanied by an increase in the adherence of gram-negative bacilli[8]. Studies of humans undergoing serious surgical operations have shown that this stress was associated with a dramatic decrease in cell-surface fibronectin and an increase in the adherence of gram-negative bacilli during incubation of buccal cells *in vitro*; these changes were associated with colonization of the oropharynx by gram-negative bacilli *in vivo*[9]. The mechanism of these changes may be mediated by an increase in the proteolytic activity of upper respiratory secretions which was shown to increase over three fold in the above experiments. The source of the increased proteolytic activity was not demonstrated.

A third mechanism of adherence occurs when molecules in secretions form a bridge between identical binding sites on both bacteria and the cell surface[2]. This mechanism may be particularly important in the gut where lectins present in food or mucus appear to provide the bridge between bacteria and mucosal cells. Although exceptions have been reported, most investigators have found that salivary constituents decrease adherence of oral bacteria. Mucins may provide binding sites in competition with cell surface receptors. Immunoglobulin A directed against oral bacteria also tends to inhibit adherence. Salivary constituents may cause agglutination of oral bacteria, a phenomenon that probably promotes clearance of organisms from the mouth[10].

Adherence and the Normal Flora

Organisms that comprise the usual bacterial flora of the oral cavity readily adhere to regional epithelial cells during brief periods of incubation *in vitro* while non-indigenous organisms do not[11]. Further, cells obtained from different sites within the oral and pharyngeal cavities demonstrate patterns of selective adherence that closely parallel the geographic differences in the bacterial flora *in vivo*. These observations, coupled with the historical observations of the constancy of the upper respiratory tract flora in a given individual[12], have established that selective adherence is a prominent, if not the major factor, in determining the composition of the normal flora.

These observations alone do not fully explain the lack of certain common organisms at this site. For example, organisms such as *E. coli* are always present in the lower gastrointestinal tract of humans and are taken into the mouth daily. Yet, colonization of the oropharynx by these organisms is uncommon among healthy individuals. Previous hypotheses on the restricted nature of the normal flora, such as selective pressure exerted by the physico-chemical milieu, would not provide an adequate explanation since *E. coli* is capable of growth in the medium of the mouth. Certain organisms indigenous to the normal oropharynx, such as viridans streptococci, have been shown to elaborate substances which are inhibitory to gram-negative bacilli *in vitro* and it has been postulated that this type of bacterial antagonism is important in preventing colonization by transient organisms[13]. While there does appear to be a reciprocal relationship between viridans streptococci and enteric organisms in the oropharynx, best shown while the former are suppressed by antimicrobial therapy, bacterial antagonism alone would not explain the rapid disappearance of the enteric organism and reappearance of viridans streptococci following discontinuance of therapy. Rather, this sequence of events appears to be best explained by an intrinsic mechanism such as selective adherence which favors colonization by only certain species. Once established on the mucosal surface indigenous organisms may elaborate inhibitory factors, consume essential nutrients, or otherwise act to prevent persistence of non-indigenous organisms. Similar complex interactions have been studied in a continuous flow system designed to mimic conditions in the gut by FRETER[14] but this type of analysis has not been applied to the upper respiratory tract.

Adherence and Colonization by Pathogenic Organisms

The role of mucosal adherence in colonization

of the upper respiratory tract by highly virulent organisms is less well established, although an important role seems likely. Most common respiratory pathogens are encapsulated and encapsulated organisms are much less likely to adhere to cells than are non-encapsulated strains of the same organism[15] Attempts to identify pathogenic pneumococci on the surface of oropharyngeal cells of colonized individuals were largely unsuccessful[16]. Teleologically, it is to the bacterium's advantage to gain a capsule when attempting to avoid phagocytosis so it may not be surprising that encapsulated strains predominate in blood, secretions, or tissues. On the other hand, loss of the capsule would facilitate adherence to regional epithelial cells and the establishment of colonization. Recent evidence suggests that bacteria can switch production of capsular material on and off rapidly in response to local conditions although the mechanisms of this control are not well understood[17]. This hypothesis would propose that organisms that persist on the epithelial surface would be predominantly non-encapsulated and thus not detected with antisera against capsular antigens. On the other hand, with tissue invasion or shedding into respiratory secretions, capsular material would be rapidly acquired to minimize adherence to and ingestion by phagocytic cells.

Alterations of the host may be important in colonization by pathogenic bacteria. Acquisition of gram-negative bacilli by both seriously ill humans and stressed experimental animals has been related to an increase in the adherence of gram-negative to buccal cells *in vitro*[18,19]. This finding appears to be associated with loss of cell-surface fibronectin which tends to inhibit adherence of these organisms if present in normal amounts. These observations indicate that receptors for gram-negative bacilli are present on the surface of normal buccal cells but that these receptors are rendered unavailable by acquisition of a surface protein. Fibronectin is not present on cells beneath the surface of the buccal epithelium and thus appears to be acquired from the secretions bathing the epithelium.

Viral infection of cells may increase the numbers of bacteria which adhere to the cell surface. Influenza A infection increased the binding of both staphylococci[20] and group B streptococci[21]. Adherence of bacteria was inhibited by prior incubation of the infected cells with antisera against influenza A but not normal sera suggesting that viral components incorporated into the cell surface provided the binding sites.

Increased binding of *Pseudomonas aeruginosa* to tracheal cells in humans has been correlated with a poor nutritional status of the host[22]. On the other hand, individuals who were presumably healthy except for recurrent urinary tract infections demonstrated greater adherence of *E. coli* to both urogenital and buccal epithelial cells, suggesting that a generalized cell surface abnormality might be responsible[23]. Susceptibility to urinary tract infection with *E. coli* which bind to globotetraosylceramide has been correlated with the presence of PI antigens on blood cells[24]. Although not directly shown, similar antigens are presumably present in urinary epithelial cells as well and form the site of bacterial attachment in susceptible individuals. Similar observations have not been made in the respiratory tract.

Summary

Selective bacterial adherence is probably the predominant mechanism determining the flora of the normal oropharynx. Colonization by highly pathogenic organisms is often preceded by events which alter normal cell surfaces, including viral infection, injury or stress, and perhaps perturbation of the normal flora by antimicrobials. Alterations of the cell surface which promote adherence of pathogenic organisms may include changes in cell membrane composition or changes in the secretions bathing the mucosal surface. It is likely that rapid phase changes in the bacteria are also operative.

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会 長 講 演

クラミジアと呼吸器感染症

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昨今，クラミジア感染症といえば，STD としての *Chlamydia trachomatis* による感染症が専ら関心を集めているようであるが，呼吸器感染症の病原微生物としては，やはり *C. psittaci*, *C. trachomatis* ともに重要である。

オウム病の臨床

オウム病の原因である *C. psittaci* は本来鳥の病原クラミジアで人にも感染する人畜共通感染症であるが，近年のペットブームと輸入鳥の増加とも相まって，*C. psittaci* による潜在的汚染はかなり広範囲に及んでいると考えられる。特にオウム・インコ類では，山下・福士らによると 70% 以上にクラミジアが分離されており，世界的にもオウム病の増加が危惧されている。

わが国のオウム病は届出の義務がなくその実態を知ることは困難であるが，SRL の資料に基づいて，CF 抗体価 32 倍以上を陽性としてみてみると，年間 250～300 名程度であり昭和 57 年以降 4 年間で特に急激な増加傾向はないようである。

オウム病の臨床症状は通常 38～39℃ の高熱，頭痛，筋肉痛など一見インフルエンザ様の症状で急激に発症し，初期には乾性咳嗽で痰を伴うことは少なく，比較的徐脈や時に発疹，肝・脾腫などを伴うこともある。胸部X線所見は特徴的で，肺門から連続して周辺に楔状に拡がる比較的淡い浸潤影として認められ，マイコプラズマ肺炎や PAP と類似した所見を呈する。

私共が経験した全症例で明らかな鳥との接触歴があり，飼育インコからも比較的高率にクラミジアを分離し得ている。セフェム系の抗生剤が無効の肺炎で，しかも鳥との接触歴がある場合には充分本症を考える必要がある。私共も 1 例死亡例を経験しており，やはり早期診断，早期治療が重要である。

クラミジアに対する血清抗体価測定

血清抗体価の測定は，川崎医科大学微生物学の松本・別所らが開発した Microplate immunofluorescence antibody technique (MFA 法) により行なった。本法は本来 genus specific であり *C. psittaci*, *C. trachomatis* の両者に反応するが，*C. psittaci* として MP 株を，*C. trachomatis* として L_2 株を用いることにより，その反応性の強弱に応じて両者の鑑別が可能である。しかもクラミジア封入体を対象とするため抗原精製の必要がなく，100 倍程度の弱拡大で観察可能である。Wang らにより確立された MIF 法は，基本小体を抗原とすることにより種特異性には優れているが，操作の点で MFA 法が簡便であり，スクリーニング検査法としては優れた方法であると考え，MFA 法により抗体価測定を行なった。

Table 1 Prevalence of serum antibodies to Chlamydiae in healthy adults and patients with respiratory tract infections

	C. psittaci	*C. trachomatis*
Healthy adults	4/100 (4.0%)	5/100(5.0%)
Upper respiratory tract infections	14/158 (8.9%)	31/158(19.6%)
Pneumonia	5/ 90 (5.6%)	12/ 90(13.3%)

Table 2 Prevalence of serum antibodies to Chlamydiae in immunocompromised patients

	C. psittaci	*C. trachomatis*
Hemodialysis	1/ 31(3.2%)	3/ 31(9.7%)
Blood diseases	0/ 23(0%)	3/ 23(13.0%)
Diabetes mellitus	1/ 18(5.6%)	5/ 18(27.8%)
Liver cirrhosis	2/ 32(6.3%)	10/ 32(31.3%)
Lung cancer	2/ 30(6.7%)	10/ 30(33.3%)
Total	6/134(4.5%)	31/134(23.1%)

成績は Table 1, 2 に示した。血清希釈 8 倍以上を陽性として示したものであるが，健康成人 100 人では，*C. psittaci*, *C. trachomatis* に対してそれぞれ 4.0% と 5.0% の陽性者がみられたにすぎなかったが，上気道炎患者 158 例では *C. psittaci* に対して 14 例 8.9%，*C. trachomatis* に対して 31 例 19.6% と高い陽性率を示した。肺炎 90 例でもそれぞれ 5.6%, 13.3% に陽性者がみられた。

さらに Immunocompromised host における *C. trachomatis* に対する陽性者は 134 例中 31 例 23.1% と高く，特に糖尿病，肝硬変症，肺癌患者で 27.8%～33.3% と高率であった。

上気道炎の原因として *C. trachomatis* による感染が高率であることは，性風俗の変化に伴う STD の一種として説明可能であるが，Immunocompromised host における高い陽性率については STD と考えることは困難であり，易感染状態に伴う既往の感染の顕性化によるものとも考え難い。

マウス感染実験

ICR マウスを用い *C. psittaci* MP 株による感染実験を行なった。経気道感染では 10^7, 10^6 IFU/ml で 100%,

10^5 IFU/ml で 60% が肺炎死したが，静脈内感染では 10^7 IFU/ml で 80%，腹腔内感染では 20% が死亡したにすぎなかった。

組織学的検討では，感染6時間後より細気管支上皮，肺胞I型細胞の腫大が認められ，間質を中心として多数の多型核白血球の浸潤が認められるが，72時間以後には単核球の浸潤が主となり実質性肺炎像を呈するようになる。またDFA染色で著明な封入体の増加を認めることができた。同時にこれら組織変化を超微形態学的にも検討した。

経気道感染時の死亡の原因は専ら肺炎死であり，肺外病変としては少数例で肝・脾に病変が認められたにすぎないが，静脈内感染群では肺，肝，脾，脳への感染が高率に認められた。

C. trachomatis B. C. E 株による同様の感染実験を行なった。経気道感染では 10^9 IFU/ml で 100%，10^8 IFU/ml で 60% が死亡したが，10^7 IFU/ml 以下では全例生存し，静脈内感染，腹腔内感染では 10^9 IFU/ml 感染でも全例生存した。

C. psittaci あるいは *C. trachomatis* による経気道感染後生存マウスについて，血清抗体価の推移を測定した。IgM 抗体価は2週後にピークを示し以後急速に低下するが，IgG 抗体価は1～2か月後にピークとなり5か月以上にわたり持続していた。

C. trachomatis による静脈内感染2週後および6週後に経気道的再感染実験を行なったが，いずれも感染防御効果は認められなかった。

以上 *C. psittaci* と *C. trachomatis* によるマウス感染実験成績から *C. psittaci* に限らず *C. trachomatis* も肺への親和性が強く，大量感染の機会があれば充分致死的肺炎を惹起する可能性があると考えられる。しかし *C. psittaci* に比べ病原性は弱く，成人において *C. trachomatis* 肺炎を発症するためには，相当大量の *C. trachomatis* に曝露されるか，あるいは高度に感染防御能が低下している状態が必要であると考えられた。

クラミジア感染症の治療

C. psittaci MP 株，患者飼育インコよりの分離株ならびに *C. trachomatis* B. E. L_2 株に対する各種抗菌剤の MIC を測定した。MINO の MIC が 0.025 μg/ml 以下と最も低く，次いで DOXY，RFP さらに新しいマクロライド系の RKM や TE-031 が優れた発育阻止作用を示した。その他ピリドンカルボン酸系の OFLX，CPFX，NY-198 などにも発育阻止作用が認められたが，GM および CPZ などセフェム系抗生剤は全く無効であった。

MINO，EM，TE-031，OFLX については，これら薬剤添加後の超微形態学的変化についても検討した。

さらに MP 株 10^7 IFU/ml 感染マウスの治療実験では，MINO が最も優れており，次いで DOXY，RFP が有効であったが，EM，OFLX ではほとんど無効であった。しかし MP 株 10^5 IFU/ml 感染マウスの治療では EM，OFLX，CPFX でも有効であり，軽症感染症に対しては充分有効性が期待できるものと考えられた。

クラミジア感染症の今後の問題点

近年新しい *C. psittaci* 株，TWAR(TW-183，AR-39)による人-人感染と考えられる呼吸器感染症が報告されている。今回 MFA 法で *C. trachomatis* に対して陽性を示した上気道炎および肺炎患者の血清を，ワシントン大学の WANG 教授のもとに送付し，TWAR に対する抗体価を測定した結果，約半数が陽性の抗体価を示し極めて興味ある結果が得られた。本邦においても，このような人-人感染と考えられる，TWAR 類似の *C. psittaci* による呼吸器感染症の存在が充分考えられるので，*C. trachomatis* による呼吸器感染の関与も含めて，広範な疫学調査による実態把握が必要である。さらに基礎的問題として患者および環境からのクラミジアの分離と抗原性の解析，さらにより特異性の高い血清診断法の確立が必要であると考えられた。