

# ORAL MANIFESTATIONS OF SYSTEMIC DISEASES

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## *Introduction*

It is of considerable interest, if one examines the literature,<sup>1-11</sup> that there are approximately 200 systemic diseases which are accompanied by oral symptoms or signs. In some instances, the stomatologic clues represent the first and sometimes even the only evidence of a systemic disorder. For example, the well-known Koplik's spots appear on the buccal mucosa a matter of 24 hours or so prior to the cutaneous eruption of measles.<sup>12</sup> It follows that recognition of this lesion is extremely helpful in untangling the otherwise nonspecific prodromal picture of rubeola. In other cases, the oral symptoms or signs may parallel complaints and clues elsewhere in the body. Thus, the appearance of an erosive lesion on the buccal mucosa just behind the commissure of the lips along with a butterfly dermatosis over the malar areas is reasonably good evidence for lupus erythematosus.<sup>13</sup> And, finally, in still other instances the oral manifestations appear after lesions occur elsewhere. Thus, in pemphigus,<sup>14</sup> to pick but one example, bullae may first erupt on the skin and, days or weeks or months later, ulcers may appear in the mouth.

It should be clear, from what has just been said, that the examination of the oral cavity can indeed contribute to the final diagnosis. The value so derived is enhanced by the fact that there are very few areas of the body which can be studied more easily and with

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fewer tools than the oral cavity. Though the eyegrounds are not usually inspected during the course of a routine physical examination, there are few physicians who will argue the importance of retinoscopy. The excuse usually offered is that this procedure is time-consuming, requires special equipment and skill, must be done under darkened conditions, and optimally after the iris has been dilated. Surveys conducted among physicians disclose that the oral cavity is also frequently overlooked. Precisely why this should be is not clear. Surely, it cannot be due to its inaccessibility, the instruments, the time factor. For it is a fact that the mouth can be surveyed in a matter of seconds under bright illumination with just a tongue blade.

## *The Diagnostic Importance of the Oral Cavity*

The question logically follows as to how important, diagnostically, is the oral cavity. The answer is that it can provide inestimable information. The answer to the question as to why the oral cavity is so important is due to the fact that: (1) it contains all of the cells derived from the primary germinal layers which form tissues found elsewhere in the body, and (2) it includes tissues and structures not demonstrable anywhere else in man.

## *Similarities Between the Mouth and*

## *Other Organs*

It is apparent that diseases which afflict other regions can also involve the oral tissues. This is true, first, because the oral, vaginal,

and rectal mucosae and the skin are embryologic cousins. Thus, it is a fact that generalized cutaneous and mucosal disorders may involve also the oral surface lining. Secondly, there are fat, cartilage, bone, and the other types of connective tissue in the mouth. These cellular aggregates are in most cases indistinguishable from their counterparts observed elsewhere. Therefore, it is not surprising that disorders of lipid metabolism, reticuloendothelial diseases, collagen disorders, and osteodystrophies are all well represented in the mouth. The important point to be underscored is that the mouth is made up of the very same types of cells and cellular aggregates found elsewhere in the body. It is reasonable to expect, and such is the case, that the afflictions will be the same.

#### *Differences Between the Mouth and Other Organs*

While, fundamentally, most of the oral cells and tissues are no different from those observed in the foot or abdomen, there are special cells and tissues which give to the mouth the singularity not found anywhere else in the entire body. Put more simply, the mouth is different both *structurally* and *functionally* from other areas. This uniqueness is best exemplified in: (1) the temporomandibular joint, (2) the teeth, and (3) the unusual physiologic role of the oral cavity.

*The Temporomandibular Joint:* This structure, by its very designation, is a joint and one would expect that it would be subject to the usual articular disorders. This is well borne out by the fact that rheumatoid arthritis, osteoarthritis and the infectious arthritides involve the temporomandibular joint just as they afflict the interphalangeal joint spaces, the elbow, or the back. But, at the same time, the temporomandibular joint is a special articulation because: (1) it is in effect two joints, (2) it is the only articulation where the right joint must always know what the left is doing, and (3) it is the only articulation which is at the mercy of the teeth. First, it is important to recognize that the temporomandibular joint is a ginglymoarthrodial articulation. This means that it possesses a hinge component and a sliding action. When one depresses the lower

jaw slightly from the point where the teeth are in occlusion, then the joint acts in a purely hinge fashion. If the mandible is further lowered, the condyle then slides downward and forward along the articular eminence of the temporal bone. The joint now demonstrates a translatory or sliding action. Thus, it is clear that there are actually two articulations which give to the joint a special significance. cursory inspection will prove that it is impossible for the right condyle to move without a change in the position of the left joint. Finally, the temporomandibular joint is at the mercy of the teeth. Should one or more teeth be malposed, then the jaw will be displaced when the teeth are brought together. Such constant microtraumata can eventually lead to arthropathy.<sup>15, 16, 17</sup>

*The Dental Apparatus:* The most obvious distinctive feature of the oral cavity is the presence of teeth and associated periodontal tissues. Little attention is generally paid to the fact that herein lies a most delicate mechanism. For example, it is not generally recognized that sheets of paper, differing from each other by a few thousandths of an inch in thickness, can be differentiated by biting down upon them.<sup>18</sup> This is largely because of a very sensitive proprioceptive mechanism housed within the periodontal membrane which envelops the roots of the teeth and a similar apparatus built into the muscles of mastication. But, from a purely pathologic standpoint, the presence of teeth creates problems not encountered elsewhere. For example, tumors of the oral cavity are benign or malignant, epithelial or non-epithelial, just like neoplasms in other regions. In addition, oral tumors are either odontogenic or nonodontogenic. This, it should be clear, creates additional diagnostic and therapeutic problems. It is safe to conclude that the oral cavity is structurally different from other areas by virtue of its dental apparatus.

*The Unusual Physiologic Role of the Oral Cavity:* It should be clear that the mouth, from evidence thus far given, is *structurally* unique. But even more important are the *functional* demands placed upon the oral cavity. Here we have a mucosal cavity, much like the vagina and rectum in its anatomic design, which is expected to perform miracles which

one would never ask of any other mucosal surface. For example, at one moment the oral mucosa must cope with the insult of boiling coffee and freezing ice cream. And, surprisingly enough, it fares well under such trauma *provided* it is in excellent health. But in the presence of slight imbalance, lesions appear in the oral cavity when no lesions are evident in any other area. The reason for this mechanism is quite clear.

There is now ample proof that disease, in general, is a function of the product of a systemic substrate and local irritating factors.<sup>19,20,21</sup> For example, a scorbutic animal will show evidence of scurvy except in the one immobilized extremity. Conversely, a scorbutic guinea pig will show more pathologic change in the one extremity to which has been attached a weight. It is common knowledge that pellagra may first become evident when the patient steps out into the sun and develops dermatitis. Obviously, the patient was just as pellagrous a moment before the cutaneous eruption. But it took the local irritation of actinic rays to produce the eruption. Since the mouth is under constant micro-traumata, it is clear why a systemic disease may first become clinically apparent by way of oral symptoms or signs.

For reasons just cited, the mouth may be regarded as an excellent barometer of disease. It is, therefore, quite understandable why over 200 systemic diseases make their clinical debut with oral complaints or observable signs.

#### *Systemic Diseases with Oral Manifestations*

Over 200 disorders which are fundamentally of a systemic nature somewhere during their clinical course, display oral findings. These disorders can be variously classified. Probably the only truly accurate classification is an alphabetic one. Thus, for example, rickets is classed under "R" and lupus erythematosus logically is characterized as "L". But, unfortunately, the patient does not come to the doctor alphabetized. Thus, such a classification, though accurate, is worthless. One fairly precise and very helpful system is that of grouping diseases in an etiologic frame. True enough, this system has inadequacies since some disorders fall into more than one niche

and others defy classification. Admitting this shortcoming, an etiologic schema is still the most realistic one. Systemic disorders with oral manifestations can be conveniently grouped into nine categories (Table 1).

*Table 1*  
*Etiologic Classification of Systemic Diseases With Oral Manifestations*

- Biologic agents
- Chemical agents
- Neoplasms
- Hormones
- Developmental factors
- Nutritional imbalance
- Reactions to stress
- Metabolic factors
- Miscellaneous

#### *Diseases Due to Biologic Agents*

There are approximately 50 infectious diseases which include oral manifestations. The causative microbe may be a bacterium, a virus, a fungus, rickettsia, protozoa, or metazoa. Some few can only be regarded as of suspected biologic origin since the clinical picture resembles that of an infectious disease but no specific agent has as yet been identified (Table 2).

*Table 2*  
*Diseases Due To Biologic Agents*  
*Causative Microbes*

- Bacteria
- Virus
- Rickettsia
- Protozoa
- Metazoa
- Suspected biologic origin

*Bacterial Diseases:* In Table 3 are listed the infectious diseases which fall into this category. In some cases, the oral lesions are quite

*Table 3*  
*Systemic Bacterial Diseases*  
*With Oral Manifestations*

- Anthrax<sup>22, 23</sup>
- Brucellosis<sup>24</sup>
- Diphtheria<sup>25, 26</sup>
- Facial erysipelas<sup>27, 28</sup>
- Glanders<sup>29, 30</sup>
- Gonococcal infections<sup>31, 32</sup>
- Leprosy<sup>33, 34</sup>
- Plague<sup>35</sup>
- Rat-bite fever<sup>36, 37</sup>
- Scarlet fever<sup>38, 39</sup>
- Syphilis<sup>40, 41</sup>
- Tetanus<sup>42, 43</sup>
- Tuberculosis<sup>44, 45</sup>
- Tularemia<sup>46, 47</sup>
- Typhoid fever<sup>48</sup>

varied and generalized in the mouth (e.g., syphilis); in other instances only one area is involved (e.g., the strawberry tongue in scarlatina); sometimes only soft tissues are im-

plicated (e.g., diphtheria); in other cases the pathologic change may occur in bone (e.g., tuberculous osteomyelitis).

*Viral Diseases:* Probably the greatest number of infectious diseases with oral findings are of viral origin. These are charted in Table 4. Sometimes the cardinal oral sign is a macule, papule, vesicle, or pustule (e.g., chickenpox). As a matter of fact, almost all of the acute exanthematous diseases can display an enanthem. The oral lesions may be the only evidence of a viral process. Space does not allow a detailed account of the many interesting points which could be elaborated upon in connection with the oral manifestations of viral diseases. Further information can be obtained by referring to the bibliography.<sup>49-78</sup> However, three points will be mentioned simply by way of example. First, the general statement can be made that one seldom if ever observes vesicles in the mouth. Actually, vesiculation is a common oral process. However, because of the thin wall and great intravesicular fluid pressure, the vesicle promptly ruptures. The end result is an ulcer. Thus, in vesiculating cutaneous diseases one is very apt to observe oral ulcers. Secondly, the oral microbial flora is highly pathogenic and, given the opportunity to invade, does so. Thus, one often notes a lesion complicated by secondary, nonspecific, bacterial invasion, and this secondary microbial invasion and inflammation make the diagnosis of oral lesions extremely difficult.

*Table 4*  
*Systemic Viral Diseases With Oral Manifestations*

Adenovirus infection	49, 50
Behcet's syndrome	51, 52
Chickenpox	53, 54
Foot-and-mouth disease	55, 56
German measles	57, 58
Granuloma inguinale	59, 60
Herpangina	61, 62
Herpes simplex	63, 64
Herpes zoster	65, 66
Lymphopatia venereum	67, 68
Measles	69, 70
Mumps	71, 72
Poliomyelitis	73, 74
Rabies	75
Smallpox	76, 77
Yellow fever	78

*Other Biologic Diseases:* For completeness sake only, Table 5 lists systemic fungal, rickettsial, protozoal, metazoal, and suspected

biologic disorders with oral manifestations.

*Table 5*  
*Other Biologic Systemic Diseases With Oral Manifestations*

<i>Fungal Diseases</i>	
Blastomycosis	79
Histoplasmosis	80, 81
<i>Rickettsial Diseases</i>	
Rickettsialpox	82, 83
<i>Protozoal Diseases</i>	
Leishmaniasis	84, 85
<i>Metazoal Diseases</i>	
Cysticercosis	86
Trichinosis	87
<i>Suspected Biologic Origin</i>	
Infectious mononucleosis	88, 89
Mikulicz' disease	90, 91
Sarcoidosis	92, 93

*Diseases Due to Chemical Agents*

Broadly speaking, the syndromes which result from chemical insult are due specifically to: (1) acids, (2) metals, (3) inorganic substances, (4) organic compounds and, inevitably, (5) a miscellaneous group.

*Acids:* Generally speaking, the acids which produce systemic diseases with oral counterparts are listed in Table 6. It is true that, in the main, these acids are either inhaled or ingested and, in so doing, they act directly upon the tooth surface. This is in contradistinction to the metals, which very frequently circulate through the blood stream and exert their effect through the saliva.

*Table 6*  
*Chemical Agents (Acids) Which Produce Systemic Diseases With Oral Manifestations*

Chromic acid	94, 95
Hydrochloric acid	96
Hydrofluoric acid	97
Nitric acid	98
Sulfuric acid	99
Tartaric acid	100

*Metals:* Many heavy metals are absorbed via the respiratory or alimentary tracts. They then exert their deleterious effects upon the oral tissues either as they circulate through the vessels of the mouth or following excretion in the saliva. In the main, most heavy metal intoxication results from an occupational hazard. This is certainly true with thallium, tellurium, vanadium, lead, and cadmium. However, it is possible that a heavy metal may be introduced as a medicament. This is sometimes the case with bismuth, gold, and mercury. The metals of particular importance to this discussion are outlined in Table 7.

*Inorganic Substances:* There are a few agents of inorganic origin which can play

*Table 7*  
*Chemical Agents (Metals) Which Produce Systemic Diseases With Oral Manifestations*

Bismuth	101, 102
Cadmium	103, 104
Gold	105
Lead	106, 107
Mercury	108, 109
Silver	110, 111
Tellurium	112, 113
Thallium	114, 115
Vanadium	116, 117

havoc with the oral tissues. In some instances, the problem arises as an occupational hazard. This is best exemplified by phosphorus intoxication. In other cases, the drug is introduced as a medicament (e.g., arsenic and bromides). One encounters mottling of the teeth in areas where excessive amounts of sodium fluoride naturally occur in the public water system. Finally, the increasing use of radioactive preparations (e.g., iodine) for the treatment of thyroid disease can lead to effects upon the salivary glands with a reduction in saliva and an increase in dental decay. Preparations which fall into this category and produce systemic diseases with oral manifestations are listed in Table 8.

*Table 8*  
*Chemical Agents (Inorganic Substances) Which Produce Systemic Diseases With Oral Manifestations*

Arsenic	118, 119
Bromide	120, 121
Fluorine	122, 123
Iodine	124
Phosphorus	125, 126

*Organic Compounds:* Contact with metals, as a general rule, is by way of occupation. In contrast, organic compounds which lead to oral pathologic changes are generally taken as medicaments. The classical example is the gingival hyperplasia in the epileptic patient associated with the use of Dilantin (diphenylhydantoin sodium). It is of interest, in this regard, that stilbamidine, originally instituted as an antimycotic drug, was found to have a selective anesthetic effect upon some of the cranial nerves. This has led to its use as a form of therapy in trigeminal neuralgia. However, in any case, the fact remains that this particular agent does indeed produce changes in and around the oral cavity when it is used in the treatment of systemic disease. The compounds of particular import have been outlined in Table 9.

*Table 9*  
*Chemical Agents (Organic Compounds) Which Produce Systemic Diseases With Oral Manifestations*

Aniline	127, 128
Dilantin	129, 130
Stilbamidine	131, 132
Benzene	133, 134

*Miscellaneous Chemical Agents:* Actually, there are a tremendous number of other chemical substances which may excite symptoms or lesions in the mouth. A number of these agents can be grouped together because they produce *aplastic anemia* and *agranulocytosis*. It is of particular interest that both of these conditions often make their clinical appearance first in the oral cavity<sup>135, 136</sup> by way of rather characteristic ulcers. It should be recalled that the usual ulcer in the oral cavity is surrounded by an erythematous margin indicating the ability on the part of the organism to combat the noxious agent by calling forth inflammatory cells. In aplastic anemia and in agranulocytosis the characteristic finding is the absence of the erythematous ring about the ulcer.

#### *Neoplasms*

Just about every primary neoplasm known to man has been found in the tissues of the oral cavity. This is quite understandable since just about every type of epithelial and mesenchymal tissue is normally present in the mouth. In addition, it is quite comprehensible that lesions which are primary elsewhere in the body may metastasize to the oral cavity<sup>137</sup> as they can to other areas. However, in keeping with the theme of this report, only the *systemic* neoplasms deserve our consideration. These are summarized in Table 10.

*Table 10*  
*Systemic Neoplasms Which Produce Oral Manifestations*

Hodgkin's disease	138
Leukemia	139, 140
Lymphosarcoma	141, 142
Multiple myeloma	143, 144
Neurofibromatosis	145, 146

#### *Hormonal Disturbances*

Almost every endocrinopathic state has its oral representation. The cardinal feature which determines the character and extent of oral pathologic change is whether the hormonal imbalance originated before or after the design of the teeth has been set and whether it

occurred prior to or following tooth eruption. Because of these unusual features, the oral cavity is frequently a highly diagnostic area in endocrine diagnosis. The glands and the specific syndromes which show oral symptoms or signs are listed in Table 11.

Table 11

*Hormonal Disturbances With Oral Manifestations*

<i>Hypophysis</i>	
Hypophyseal gigantism	147, 148
Acromegaly	149, 150
Hypophyseal dwarfism	151, 152
Albright's disease	153, 154
(Polyostotic Fibrous Dysplasia)	
<i>Thyroid</i>	
Hyperthyroidism	155, 156
Cretinism	157, 158
Myxedema	159, 160
<i>Parathyroid</i>	
Hyperparathyroidism	161, 162
Hypoparathyroidism	163, 164
<i>Adrenal</i>	
Addison's disease	165, 166
Hyperadrenalism	167
<i>Pancreas</i>	
Diabetes mellitus	168, 169
<i>Gonads</i>	
Puberty	170, 171
Menstruation	172, 173
Pregnancy	174, 175
Climacteric	176, 177
Chronic desquamative gingivitis	178, 179

Hypopituitarism and hypothyroidism early in life often lead to retarded eruption of the teeth. Conversely, hyperpituitarism and especially hyperthyroidism and hyperadrenalism produce precocious dental eruption. In addition, many soft tissue changes become evident. Thus, the tongue enlarges in cretinism and acromegaly, prognathism is common with hyperpituitarism, pigmentary changes occur with hypoadrenalism, enamel hypoplasia is part of the rachitic picture, and periodontoclasia is seen with diabetes mellitus, puberty, menstruation, pregnancy, and the climacteric.

*Developmental Disturbances*

Inherited disorders and those acquired congenitally may fall into two categories: (1) systemic developmental problems with *non-specific* oral changes, and (2) systemic developmental disturbances with *specific* oral

Table 12

*Systemic Developmental Disturbances With Nonspecific Oral Manifestations*

Congenital heart disease	180
Cooley's anemia	181, 182
Hemophilia	183, 184
Intestinal polyposis	185, 186
Muscular dystrophy	187, 188
Progeria	189
Sickle cell anemia	190, 191

symptoms and signs.

In the first group, charted in Table 12, there are oral symptoms and signs. However, the oral findings are not pathognomonic of a specific disease process. For example, there are nondescript macules associated with intestinal polyposis, gingival bleeding with hemophilia, and osteoporosis with sickle cell anemia. In contrast, the intraoral findings in the second group are quite characteristic and sometimes may be the pathognomonic clue to the final diagnosis. For example, the opalescent teeth in osteogenesis imperfecta are highly diagnostic since this oral finding is not observed in any other disorder. These systemic diseases with specific oral symptoms and signs are charted in Table 13.

Table 13

*Systemic Developmental Disturbances With Specific Oral Manifestations*

Achondroplasia	192, 193
Albers-Schonberg disease	194, 195
Cleidocranial dysostosis	196, 197
Hereditary ectodermal dysplasia	198, 199
Osteogenesis imperfecta	200, 201

*Nutritional Disturbances*

Nutritional states may be of two kinds: (1) excess nutrition, exemplified by obesity and hypervitaminoses A and D, and (2) deficiency states. The latter are more relevant to the present discussion and the diseases of particular interest are outlined in Table 14. In the main, deficiency states produce changes in the teeth only if the disorder prevails in early life during the developmental period in dental maturation. In later years, the principal findings of nutritional deficiency states are noted in the soft tissues and in the bone.

Table 14

*Nutritional Deficiency States With Oral Manifestations*

Vitamin A	202, 203
Thiamine	204, 205
Riboflavin	206, 207
Niacin	208, 209
Pyridoxine	210, 211
Ascorbic acid	212, 213
Vitamin D	214, 215
Vitamin K	216, 217
Sprue	218, 219
Pernicious anemia	220, 221
Iron	222

*Reactions to Stress*

It is only in recent years that the health professions have come to recognize the role of stress in disease in general and especially in

the causation of oral disease.<sup>223, 224</sup> In one sense of the word, all disease states represent a reaction to stress. But even in its more limited connotation, it is a fact that physical factors, psychologic circumstances, and allergic phenomena must be considered in this category. There are a number of such problems which involve the oral structures. These have been listed in Table 15. In some instances, the cardinal findings appear in the dentition and periodontal tissues. This is evidenced by marked abrasion of the teeth in bruxism, in thickening of the periodontal membrane in scleroderma, by changes in jaw development and occlusion in rheumatoid arthritis. In other cases, the soft tissues are principally involved. Thus, one finds swelling in angioneurotic edema, erosive lesions in erythema multiforme, lace-like white lines with lichen planus.

*Table 15*

*Stress Reactions With Oral Manifestations*

Angioneurotic edema<sup>225, 226</sup>  
 Anxiety<sup>227, 228</sup>  
 Bruxism<sup>229, 230</sup>  
 Erythema multiforme<sup>231, 232</sup>  
 Erythema nodosum<sup>233, 234</sup>  
 Erythroblastosis fetalis<sup>235, 236</sup>  
 Lichen planus<sup>237, 238</sup>  
 Lupus erythematosus<sup>239, 240</sup>  
 Polyarteritis<sup>241, 242</sup>  
 Psoriasis<sup>243, 244</sup>  
 Rheumatoid arthritis<sup>245, 246</sup>  
 Scleroderma<sup>247, 248</sup>

*Metabolic Disorders*

In the strictest sense of the word, all disease states can be regarded as showing evidence of a metabolic disturbance. But, in a more limited sense, there are conditions in which the cardinal or primary derangement is one of metabolism. This is admittedly a controversial category. However, for practical pur-

*Table 16*

*Metabolic Disorders With Oral Manifestations*

*Primary Lipid Storage Diseases*

Gaucher's disease<sup>249, 250</sup>  
 Niemann-Pick's disease<sup>251, 252</sup>

*Secondary Lipid Storage Diseases*

Eosinophilic granuloma<sup>253, 254</sup>  
 Hand-Schuller-Christian's disease<sup>255, 256</sup>  
 Letterer-Siwe's disease<sup>257, 258</sup>

poses and in terms of stomatologic disease, metabolic disorders may be regarded as being primary or secondary in nature. Those with stomatologic overtones are summarized in Table 16.

*Miscellaneous Disorders*

In Table 17 are listed a number of such diseases which are associated with significant changes in the oral cavity. The general statement can be made that in no instance are the oral findings pathognomonic. However, the presence of such clues in addition to other observations made elsewhere in the body is the constellation which leads to a correct final diagnosis.

*Table 17*

*Miscellaneous Disorders With Oral Manifestations*

Amyloidosis<sup>259, 260</sup>  
 Mongolian idiocy<sup>261, 262</sup>  
 Myasthenia gravis<sup>263, 264</sup>  
 Myotonia atrophica<sup>265</sup>  
 Paget's disease of bone<sup>266, 267</sup>  
 Pemphigus<sup>268, 269</sup>  
 Pityriasis rosea<sup>270</sup>  
 Plummer-Vinson syndrome<sup>271, 272</sup>  
 Polycythemia<sup>273</sup>  
 Sjogren's syndrome<sup>274, 275</sup>

*Summary*

1. The oral cavity is like and unlike other areas of the body. It therefore follows that the mouth is subject to many of the ills found elsewhere and, at the same time, may be afflicted with disorders not observed in any other part of the body.

2. In the main, the general statement can be made that a systemic disease is apt to make its clinical debut in an area under considerable trauma. Since the mouth is subject to constant microtraumata, it is clear that oral symptoms or signs may be the first evidence of a systemic disease.

3. An attempt has here been made to survey the entire field of stomatologic manifestations of systemic diseases. (An extensive bibliography is available from the author.)