

PRIMARY HERPETIC GINGIVO - STOMATITIS
Clinical Studies from General Practice

Thesis presented for the Degree of
Doctor of Medicine

by

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Frontispiece



"The crying child indeed his fingers brings
Within his mouth, whence humour constant springs
To press the gums, that swell with gnawing pain"

Sainte-Marthe

La Paedotrophia

1584

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P R E F A C E

"... studies have established this disease (herpetic gingivostomatitis) as a well defined clinical and etiologic entity" (Buddingh et al. 1953)

"It is seldom diagnosed correctly in the home"

(MacGregor 1960).

During my early years in General Practice, I became aware of a condition about which I had learned nothing as an undergraduate student. The disease, which affected young children in my practice, was associated with systemic disturbance, and with ulceration of the mouth. The constitutional upset was at times severe. Because I had worked in a busy children's hospital, I was the more perplexed by my lack of knowledge. Discussions with fellow practitioners showed that I was not alone in this: some regarded the disease as a form of "Trench mouth", others again suggested a fungous origin, akin to thrush. Vincent's angina I knew as a disease "now rarely seen, but used to occur, mainly in adults" (Card 1957), and also thrush, together with a number of rarities; but the condition I was now meeting did not fit nicely into any of these clinical categories, and it was not rare. My knowledge of the disease was acquired slowly, and, at times /

times, painfully. DIES

A night call summoned me from my bed to a distraught mother. Hollow-eyed with sleeplessness, she roundly berated me because my medicine had failed to cure her eighteen-month child's "trench mouth" (sic) for which she had consulted me two days previously.

The order in which the results are presented differs slightly. Under such stimuli, my knowledge developed from a dim awareness to the realisation of the existence of a clinical syndrome.

Phase 1. All febrile illnesses in children under twelve years whom I saw in day-to-day work were surveyed in a prospective study lasting one year. Further investigations in my patients suggested that their uniform clinical appearance was associated with a uniform pathogenic agent. Recourse to the literature confirmed that I had been dealing with "primary herpetic gingivo-stomatitis" - one of the syndromes resulting from initial infection of a susceptible person by the herpes simplex virus. Why should such a syndrome, fairly fully described, and the subject of considerable laboratory studies over the past thirty years, be so little known among family doctors? Was this a local phenomenon, or did this gap exist elsewhere? If, as I suspected, the disease was not a rarity in British National Health Service family practice, what factors kept it from being more widely recognised?

AN/

AN OUTLINE OF STUDIES

By a series of studies carried out over three years this thesis attempts to answer these questions, and to provide data on the epidemiology and aetiology of the disease as it is seen by one family doctor in a group partnership.

The order in which the results are presented differs slightly from the actual sequence of the investigations which were performed in six phases.

- In addition to antibody studies, various factors of possible aetiological significance were surveyed in a prospective study lasting one year.
- Phase 1. All febrile illnesses in children under twelve years whom I saw in day-to-day work were surveyed in a prospective study lasting one year.
- Phase 2. During the next two years, clinical details were recorded on all children who developed mouth ulcers at some stage in the course of a febrile illness.
- Phase 3. When the clinical features of the cases of "febrile stomatitis" had been more clearly defined in this way, the information obtained during phase 1. was re-examined. Analysis of this material forms the basis of the section on the clinical features and of the occurrence of the disease in general practice.
- Phase 4. /

- Phase 4. Virus studies on a sample of the cases in phase 2. showed them to be herpetic in origin. It seemed possible that all the children in the whole series had suffered from primary herpetic stomatitis. To confirm this, in retrospect, virus antibody levels were determined in as many children as possible at the close of the survey, and in particular control children. The mothers of all these children also had their antibody levels estimated. In addition to antibody studies, various factors of possible aetiological significance were compared in the index and control groups. Information was obtained on sequelae of the disease in a short-term follow-up study.
- Phase 5. A controlled retrospective study with longer follow-up was made on cases of probable herpetic stomatitis obtained by examination of records of certain children in the group practice.
- Phase 6. Finally, the family doctor's view of the disease was compared with that of the infectious diseases hospital physician during the three years of the study.

George Wiggan & ... Applied Fig. 1.

ACKNOWLEDGEMENTS

My interest was stimulated by Dr.R.H.A.Swain, Virology Department, University of Edinburgh. His colleagues, Dr. John Peutherer and Dr. Isabel Smith, encouraged my importunings, and went far beyond what any family doctor could reasonably expect in co-operation. My partners, and in particular Dr.E.V.Kuenssberg, by their continual support and encouragement helped me to sustain interest in the project at a time when the "crisis in general practice" tended to kill any extra endeavour.

This work would have been impossible without the co-operation of my patients: those who acted as "controls", and who realised they stood to gain nothing from my venepunctures, never hesitated to offer themselves and their children.

Among the many others to whom I am indebted, I wish to thank for their guidance Professor N. Grist and Dr.C.Ross, Department of Virology, University of Glasgow, and Dr.M.Moffat, Wellcome Virus Laboratory, City Hospital, Edinburgh. Dr.G.Sangster of that hospital made available to me the case notes of the patients of the hospital series also studied during the survey.

George/

George Wimpey & Company Limited supplied Fig. 1.

The photographic equipment was loaned by the South-East Scotland Faculty of the College of General Practitioners.

My thanks are due to Mrs. D. Harcus, Practice Administrative Secretary for her help and for typing.

It is of interest to note that misunderstanding exists between different workers even to-day: "aphthous ulcers of children" and "recurrent aphthous ulcers" are confused in at least one recent report (Stuart-Harris 1966).

Terminology: aphthae and herpes

It is possible to trace the term "aphthae" back to Hippocrates: "The diseases of the newborn and of infants are *ἀφθαῖ*, vomiting, insomnia" It is not so certain, however, what was meant by the term. Some indication of its meaning for the early Graeco-Roman school is afforded by the following quotation from Celsus (25BC-40AD)

"verum ea longe periculosissima sunt ulcera,
quae aphthae Graeci appellant, sed in pueris
haec aetate contingunt, in viris et

HISTORICAL/

ulcera a gingivis incipiunt . . ."

Later /

Later writers used the HISTORICAL a fairly wide range of

conditions and Paulus Aegineta (9th century AD) introduced a

It is unlikely that the condition which is known to-day as "primary herpetic gingivo-stomatitis", or "acute aphthous ulceration of children" is a new disease. Unfortunately, both the words "herpes" and "aphthae" have changed their meaning with the passage of time. The path of the would-be historian is thus beset with difficulties; it is of interest to note that misunderstanding exists between different workers even to-day: "aphthous ulcers of children" and "recurrent aphthous ulcers" are confused in at least one recent report (Stuart-Harris 1966).

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"verum ea longe periculosissima sunt ulcera,

quas apthas Graeci appellant, sed in pueris:

hos enim saepe consumunt, in viris et

mulieribus idem periculum non est. Haec

ulcera a gingivis incipiunt...."

Later /

Later writers used the term for a fairly wide range of conditions and Paulus Aegineta (7th century AD) introduced a clinical classification based on the colour of the lesion, "white, red or black": it is possible that his "black apthae" was either cancrum oris or diphtheria.

This classification stood until the Middle Ages, being merely echoed by Avicenna and others of the Arabian School. (Still 1931).

In the first of the paediatric incunabula Bagellardus (1472) writes "De pustulis sive alcola oris", and Metlinger (also 15th century) recognised "blisters in the mouths of children".

It is possible that these refer to the vesicular nature of the earliest lesions of herpetic stomatitis.

Thomas Phaire (1545) "the father of English Paediatrics", included in his "Booke of Chyl dren" an account of oral lesions which is worth reproducing, not only because it was the first description to be published in English but also because of its intrinsic merit.

"...many tymes by reson of corrupcion of the milke, venimous vapoures arising from the stomake, & of many other infortunes there chaunceth to brede a caker in ye mouthes /

mouthes of childre, whose signes are manifest ynough, ye is to saye by stinking of the mouthe, peyne in the place, contynual rennyng of spittle, swellynge of the cheke, and when the mouth is opened against the sonne, ye maye se clereye where the canker lieth. It is so named of the latter sort of phisicions, by reason of crepynge and eatynge forward and backward, and spreadeth it selfe abrode, lyke the feete of a creues, called in latine cancer, notwithstanding I knowe that the Greekes, and auncient latynes, gyve other names unto thys dysease, as in callynge it an ulcer, other whyles aphthe, nome, carcinomata, and lyke, which are al in englyshe, knowen by the name of canker in the mouthe, and although there be many kindes according to the matter whereof they be engendred, and therefore require a diversitie of curing, yet for the moste parte, whan they be in childerne, the cure of them al differeth very litle or nothing....."

Würtz (1563) clearly differentiates thrush from other forms of stomatitis:

"Sometimes there rise blisters on the tongue, and also on the cheeks within ... care must be had to be sure whether it be the beginning of a thrush..."

With the advent of the 17th century, the authority of the Classical teachers began to be questioned. Diphtheria, which had probably been included under the heading "aphthae", now began to be distinguished (Bartholin 1646). The nature of infection/

infection was increasingly appreciated, and Ballexserd, an eighteenth century physician, wrote on the dangers of allowing children to be kissed by all and sundry, because he believed various diseases might be transmitted thereby (Still 1931).

"Aphthae are found chiefly in children", writes Herberden senior (1802), and his further description suggests a relationship with respiratory catarrh.

Nearer our own time and place, Keiller (1862), discussing his own experience of cancrum oris in Edinburgh, classifies mouth lesions of children into three groups: aphthous stomatitis, ulcerative stomatitis (which he calls noma), and gangrenous stomatitis (or cancrum oris).

In 1873, the infectious nature of herpes labialis was demonstrated by Vidal, and by the beginning of the present century clinicians were beginning to suspect the herpetic origins of lesions of the mucous membrane (Cooley 1924).

The term "herpes", derived from the verb **ΕΡΠΕΙΩ** ('to creep') was originally applied to spreading cutaneous lesions, usually ulcerative, such as skin cancer and lupus vulgaris, and it has been used in medicine for at least twenty-five centuries. Long (1933) states that the first reference to herpes in the English language appears in a fourteenth century translation of a Bartholomaeus Anglicus' manuscript. Beswick (1962) traces the changes in meaning of/

of the term through the years. He considers the epithet "creeping" to be far more appropriate to the original diseases for which it was used than it is to any of the conditions which we know as "herpes" to-day.

Herpetic Stomatitis

It was not until 1932 that the first report was published of the successful isolation of herpes simplex virus from one case of stomatitis (Youmans 1932). The following year, Long (1933) isolated the virus from three cases. Because the virus could be isolated from mouths of apparently normal people, these early reports on small numbers of cases made little impact. Dodd and her co-workers (1938) reported a much larger series, and they regarded herpetic stomatitis as a clearly defined clinical entity caused by the herpes simplex virus. Such doubts as remained concerning the aetiological significance of the virus were dispelled when Burnet and Williams (1939) not only isolated the virus but also showed the development of neutralising antibodies in children with stomatitis. "This discovery", writes Durand(1948) "necessitates a review of the entire subject of mouth diseases in childhood". Black (1942) goes further: "acute infectious gingivo stomatitis (Vincent's stomatitis, Vincent's angina, ulcerative or ulcero membranous stomatitis, fusospirochetal stomatitis, trench mouth) is caused by the herpes simplex virus. The disease should now be known as acute herpetic gingivostomatitis."

Perhaps the enthusiasm to simplify the classification outstrips the supporting evidence at present available, but there are now grounds for believing that the condition with which this thesis is concerned is caused by a single agent - the herpes simplex virus.

Clinical features are particularly well described by Scott *et al.* (1941) in a group of twenty-one cases

Time - and space in retrospect. Most clinical accounts, if

they are not clear that this disease is not only rooted in history but it is also widespread throughout the world at the present time. There are publications from America (Scott *et al.* 1941) Australia (Anderson and Hamilton 1949) Finland (Halonen 1955) France (Bolger and Tenthoin 1965) Great Britain (Dudgeon 1950) Russia (Antonova 1960) South Africa (Hansen 1961) and Yugoslavia (Juretić 1960), among other countries.

A section of the thesis describes observations on a group of patients who had no such preliminary sorting. They were selected on fairly rigid clinical criteria; the evidence for considering the uniformity of the group is discussed on pages 31 to 34.

MATERIAL AND METHODS

The cases and families studied were drawn from a large National Health Service (N.H.S.) general practice of one of seven doctors working in a group partnership, with a combined total list of approximately 20,500 patients. The practice

CLINICAL FEATURES /

CLINICAL FEATURES

Several accounts of acute primary herpetic gingivostomatitis have been published since the first large series of Dodd et al. (1938). The clinical features are particularly well described by Scott et al. (1941) in a group of twenty-one cases carefully reviewed in retrospect. Most clinical accounts, if they are not merely appendages to laboratory studies, are written in this way. While such work is most valuable to the paediatrician, it is precisely this "hindsight" view which restricts its usefulness to the family doctor, concerned as he is with sorting previously unselected clinical material on the basis of the earliest manifestations of disease.

This section of the thesis describes observations on a group of patients who had no such preliminary sorting. They were selected on fairly rigid clinical criteria; the evidence for considering the uniformity of the group is discussed on pages 81 to 84.

MATERIAL AND METHODS

The cases and families studied were drawn from a large National Health Service (N.H.S.) general practice of one of seven doctors working in a group partnership, with a combined total list of approximately 20,500 patients. The practice was/

Fig. 1.



Part of the practice area.

was set in a semi-industrial area with large housing schemes composed mainly of new dwellings (Fig.1). The age and sex distribution of the whole practice population shows a greater proportion of children compared with the Scottish population pyramid (Appendix 1). Most of the patients belonged to Registrar General Social Groups iii, iv and v. The practice population did not remain static during the three years of this study. The annual turnover of patients (about 12 per cent) increased slightly in the last year, as "prefabs" were replaced by permanent buildings. The dynamics of the practice population are shown in Appendix 2.

The intimate nature of group general practice, with an interchange of some patients between partners, precludes an accurate statistical assessment of the "list size" of only one member of the partnership. Nevertheless, it is reasonable to estimate that the patients studied were drawn from a population of about 3,000 with an age and sex distribution similar to that of the whole practice, roughly one third of which was composed of children under twelve years of age.

Cases of stomatitis were not referred to me by my partners when they became aware of my interest. It occasionally happened that one of my patients was seen "out of hours" by a partner, and was then referred back to my care in the normal course/

course of events.

From 1 November 1963 to 31 August 1966, a prospective survey was made of all children whom I saw at my surgery or in their homes, who were suffering from the combination of fever and mouth ulcers. Children were included if they were under twelve years of age and if they developed at some time in the course of a febrile illness lesions of the tongue or mucosal surface of the mouth and gums. Certain obvious lesions were to be excluded, such as moniliasis or the sublingual ulcer of whooping cough, and recurrent simple aphthae (see p 91). Because of the confusion of nomenclature - Sircus et al. (1957) list eleven synonyms for the aphthous group - it is important to define the terms used in studies of oral pathology. In the present work, the mouth lesion was usually a break in the continuity of the mucous membrane, though a small vesicle was not excluded. The lesion was to be self-limiting, healing within a few days without scarring. A previous history of oral ulceration would have excluded a child, but in the event this applied to only one child who was already in the survey. The clinical illnesses were all first episodes. The age and sex of each child was noted, together with the date of onset of the illness, and the presenting symptoms. Some of the oral and cutaneous lesions were photographed.*

RESULTS /

* The equipment used was a Kodak "Colorsnap" camera, with a technical close-up outfit, employing Kodachrome ii 828 film and PF 1^D blue flash-bulbs.

RESULTS

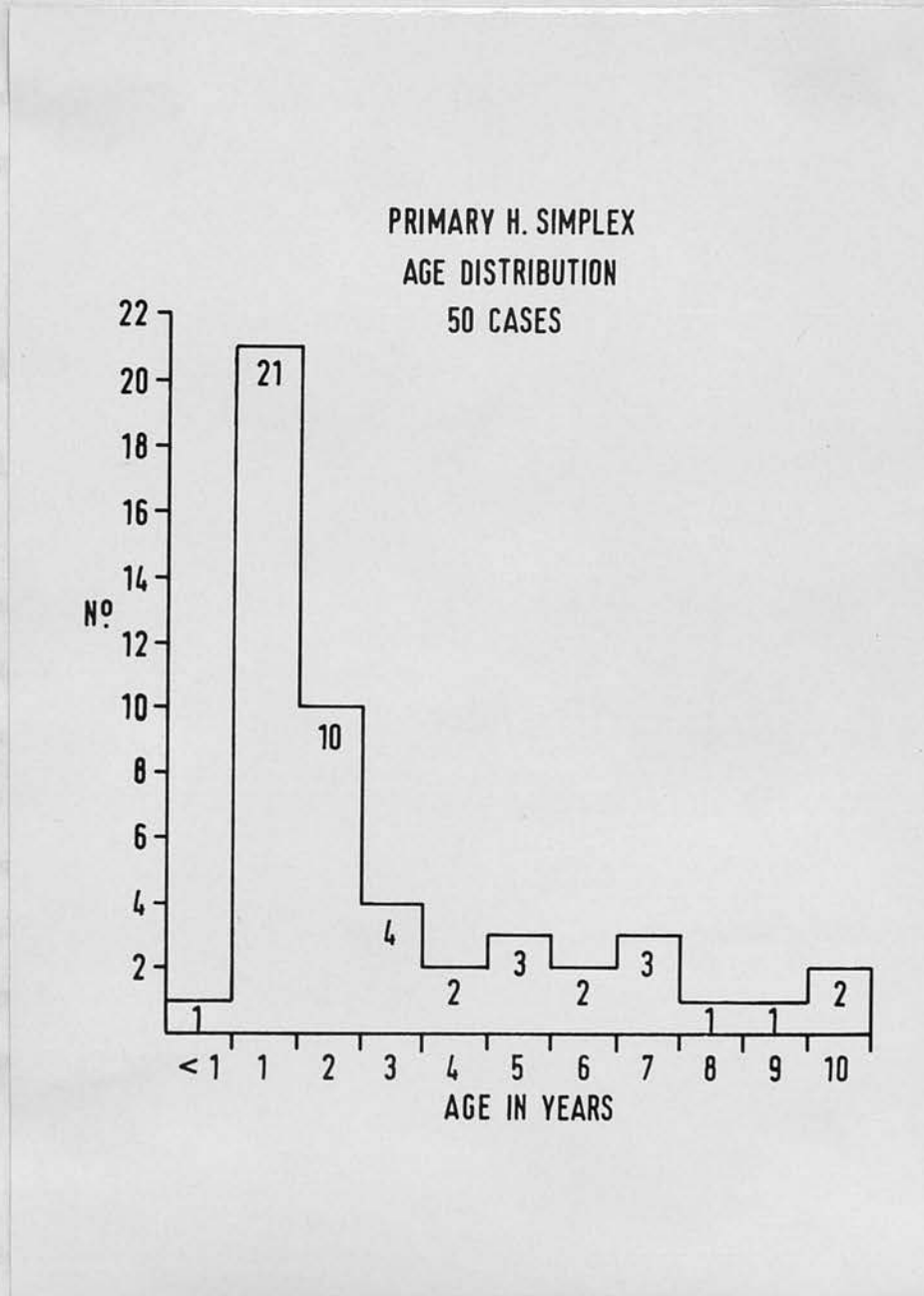
Although the clinical criteria appear cumbersome, no difficulty was found in applying them. They excluded only a dozen children, most of whom had thrush.

During the survey, fifty children were entered into the study. The clinical criteria used might be expected to allow the inclusion of a number of different diseases, the diagnosis of which would become obvious in time. However, each case was carefully reassessed in retrospect and the degree of clinical uniformity was such as to justify the analysis of the features of the group as a whole. The children were entered into the survey at all seasons of the year. The seasonal incidence of the group, illustrated in Appendix 3, shows no statistically significant difference between summer and winter.

Cases were scattered widely throughout the practice area, and such concentrations as occurred were in those streets where lived young families I usually attended. The geographical distribution of some of the cases is shown in the map (Appendix 4).

The age distribution of the fifty children shows a marked peak in the second and third years of life (Fig.2) in contrast to the age distribution of the exanthemata. This difference is illustrated in Appendix 5, which is based on experience in the first year of the survey, when details were recorded on all febrile /

Fig. 2



febrile children seen.

The distribution by sex at the different ages shows no statistically significant difference between boys and girls (Appendix 6).

PRIMARY H. SIMPLEX
DEGREE OF PYREXIA
27 CASES

PRESENTING SYMPTOMS

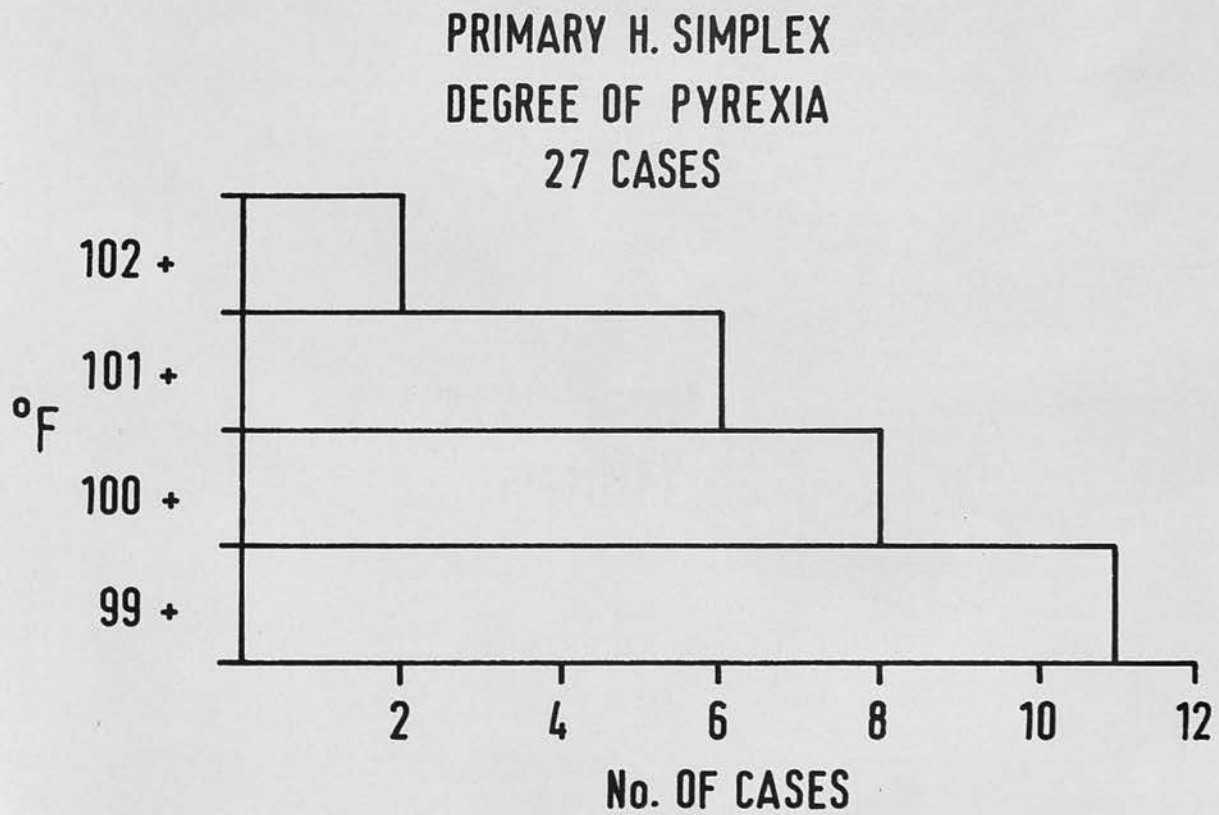
Systemic Upset

The earliest feature was the development of malaise, occasionally of marked severity. Nineteen children were judged by their parents to be too ill to be brought to the consulting room. Ten children had a history of less than one day's illness, and one, indeed, had been ill for only two hours! On the other hand, the illness developed much more gradually in a further ten children, most of whom were said to have had rather protracted "colds", which merged imperceptibly into the stomatitis.

The temperature was usually raised at this stage, and even those twenty-seven patients who were not obviously febrile were found to have some degree of pyrexia (Fig. 3).

Respiratory Catarrh /

Fig. 3.



fully active. Twisting was noted in only one patient, but atypical pain was an occasional complaint, which was relieved by the patient. A further patient had such a severe pain which was relieved by the administration of "injection" of morphine.

Respiratory Catarrh

A running nose, dry cough and faucial injection were early features, common to all the cases. They were especially prominent in eleven children who showed no feature other than pyrexia at this stage. The "heavy eyes", and respiratory catarrh in a pre-school child occasionally raised the suspicion of prodromal measles.

Alimentary Symptoms

Anorexia, a feature common to all the children, appeared early. At first this was part of the constitutional disturbance, but later on it was reinforced by the pain in and around the mouth. Salivation then became excessive, and the presence of a saliva-soaked bib round the neck of a fevered eighteen-month child is almost pathognomonic of the disease. Halitosis was not an early feature, but after the first week it was encountered fairly often. Vomiting was noted in only one patient, but abdominal pain was an occasional complaint, which was prominent in two patients. A further patient had such frequent loose stools that a tentative diagnosis of "infectious enteritis" was made.

The /

The main feature common to all the fifty patients was the development, ultimately, of mouth ulcers, which are described more fully on page, 22 .

Skin Manifestations

Although approximately one half of the patients exhibited various cutaneous phenomena, they were the presenting symptoms in only two. A boy of seven years attended for what at first appeared to be a simple pyogenic paronychia of the left index finger. His mother remarked only casually that he seemed unduly "hangy" after a cold, and the ulcers on the buccal aspect of the cheeks were found on examination. The second patient, a boy of eighteen months, developed a morbilliform rash, followed one week later by the mouth ulcers.

Parental Anxiety

One of the particularly distressing features was the evident misery of the child. It is understandable that ten days, and, worse, ten nights, of the constant fretfulness /

fretfulness illustrated in Fig.4, will strain the reserves of even the most stable parents. Sleeplessness and anxiety may then combine to engender hostility in the less well-endowed parent when there is no immediate improvement in the child's condition following the initial consultation. Such situations, though not encountered frequently, called for much patience and tact in the management of the family situation.

CLINICAL FINDINGS /

Fig. 4



H.P. ♂ 1½ Case No.35

Ulcer mucosal surface lower lip

Herpes simplex virus isolated.

Fig. 5.



Vesicle on tongue; swollen fissured lower
lip and peri-oral lesions.

Herpes simplex virus isolated.

M.B. ♀ 9 yrs. Case No. 39

Vesicle on tip of tongue.
Contiguous ulcer mucosal surface lower lip.
Herpes simplex virus isolated.
Complement fixation titres 1/32 → 1/256

Fig. 6.



M.D. ♂ 1 year. Case No.34

Vesicle on tongue: swollen fissured lower
lip and peri-oral lesions.

Herpes simplex virus isolated.

Tongue: fissured show vesicle roofs still
intact.

CLINICAL FINDINGS

Fig. 7.

Mouth Ulceration

This finding, common to all fifty patients was obvious in thirty-four of the patients. It was first observed on the first day of the onset of illness. The lesions were observed to be at the corners of the mouth (Fig. 5) which is shown in Fig. 6. The lesions on the lip on the first day and the tongue on the second day were hard pale plaques which were surrounded by a narrow zone of erythema leaving a central area of ulceration to eight to ten millimeters in diameter by a narrow zone of erythema. The lesions gradually diminished in size and disappeared in seven to ten days. Some of the local lesions were surrounded by a narrow zone of erythema and gradually disappeared in seven to ten days. Some degree of inflammatory changes was observed in the gums of most of the children, but this was not as constant or as marked as the oral lesions would suggest.



Same child as in Fig. 6.

To show umbilicated lesion on upper lip.

Tongue lesions show vesicle roofs still

Regional Lymphadenopathy

intact.

Tender enlargement of submental and submandibular nodes was a characteristic feature after the oral lesions had appeared: this /

CLINICAL FINDINGS

Mouth Ulceration

This finding, common to all fifty patients was obvious in thirty-one instances, appearing usually within 2 - 3 days of the onset of symptoms. The "ulcers" were occasionally observed to be at the vesicular stage. This is illustrated in Fig.5. which shows in addition a contiguous ulcer on the buccal aspect of the lip on the same side as the tongue vesicle. Tongue, lips, gums and the buccal aspect of the cheeks were the usual sites; the hard palate was not involved and only one patient exhibited ulcers on the fauces. The roof of the vesicle soon disappeared, leaving a round or oval greyish white ulcer 1-2 mm. across. Six to eight such ulcers were often seen, and each was surrounded by a narrow zone of erythema. They looked painful, and salivation was marked, but after 2-3 days the pain gradually diminished, although the ulcers were not much changed in appearance. In the following 3-4 days healing progressed, and the local condition usually resolved in about ten days. Some degree of inflammatory change was observed in the gums of most of the children, but this was not as constant or as marked as the term gingivo-stomatitis would suggest.

Regional Lymphadenopathy

Tender enlargement of submental and submandibular nodes was a characteristic feature after the oral lesions had appeared:
this /

Fig. 8.



Same child as in Fig. 6.

Scattered macules on R. cheek.

this lymphadenopathy had usually subsided within a week.

Fig. 9.

Skin Lesions

Half of the patients exhibited a variety of cutaneous lesions, localized and general. The general localized eruptions were seen

on the face
vesicles on
umbilicate
erythematous
three inch
appearing
were usual
-ing double
closely-pro
narped lab



well scattered
they were
erely
In at least
ring signs,
acial lesions
This interest:
er, with
e adult

Diffuse
patient was
The child,
rash, with

limited to the
ed (page 16).
rebellis-like
otic

prescribed during the prodromal stage of her illness. Another
child, aged four M.B. ♀ 9. Ulcer on tongue and
during the conv grouped lesions on chin. case, sixteen days after
six onset. She had received only paediatric aspirin mixture N.F.

Other Features /

this lymphadenopathy had usually resolved within a week.

Skin Lesions

Half of the patients exhibited a variety of cutaneous lesions, localised and general. The commonest localised eruptions were seen on the face. Situated around the mouth, they were small scattered vesicles on an erythematous base (Fig.6); sometimes they were umbilicated (Fig.7). Occasionally the lesions were merely erythematous macules on the chin and cheeks (Fig.8). In at least three instances, these macules were the first localising signs, appearing before mouth ulceration was evident. The facial lesions were usually scattered, but one child (Fig.9) showed the interesting combination of the infantile oral lesions together with closely-grouped facial lesions resembling the familiar adult herpes labialis.

Diffuse rashes were seen in two children, in addition to the patient exhibiting a morbilliform rash already mentioned (page 16). One child, aged three years, also showed a transient rubella-like rash, which could have been a drug reaction to antibiotic prescribed during the prodromal stage of her illness. Another child, aged fourteen months, developed transient urticaria during the convalescent stage of her illness, sixteen days after its onset. She had received only paediatric aspirin mixture N.F.

Other Features /

Fig. 10.



Same child as in Fig. 8.

Multifocal lesion right little finger.

Discussion

The "herpetic" "complication" observed was the development of residual lesions in seven patients. The third case involved a severe outbreak, and the Fig. 11. was illustrative of a lesion, as well as the facial vesicles, hyperemic zone and crusted



R.W. ♂ 2 years: one month
 convalescent herpetic stomatitis.
 Residual inflammatory skin changes
 round left orbit.

Other Features

The commonest "complication" observed was the development of digital lesions in seven patients. The thumb was involved in three instances, and the frontispiece illustrates such a lesion, as well as the facial vesicle, hypertrophied gums and evident misery of the child. The multifocal nature of the lesion, which was seen occasionally, is shown in Fig.10.

Whilst the condition of most of the patients settled within ten days, four patients had not regained their previous good health even after two months. In this time they remained irritable, and although the mouth ulceration had settled, the facial lesions remained evident, becoming rather eczematous in appearance. Eventually, all the children settled down. Apart from their irritability none of the patients showed evidence of meningo-encephalitis.

Other features encountered were kerato-conjunctivitis (without the formation of dendritic corneal ulcer) and periorbital cellulitis (Fig.11). The incidence of these complications is shown in Table 1.

The epidemiology and the clinical setting both strongly suggested that the cases in this series had a uniform aetiology in which the herpes simplex virus was implicated.

The /

Table 1.

COMPLICATIONS

PRIMARY H. SIMPLEX 50 CASES

DIGITAL VESICLES	7
RELAPSING COURSE ($> \frac{2}{12}$)	4
KERATO-CONJUNCTIVITIS	1
PERI-ORBITAL CELLULITIS	1
URTICARIA	1

The disease was seen to be infectious. Herpes stomatitis
 syndrome occurred in another member of the household of the same
 weeks in five instances. Table 2. Infectivity was determined
 criteria, the secondary attack rate was about 5%.

HERPETIC STOMATITIS.

* SECONDARY ATTACK RATE WITHIN AFFECTED FAMILIES

AGE (YEARS)	No. OF SIBS AT RISK	No. OF SIBS INFECTED AFTER FIRST CASE
<1	5	0
1	5	1
2	7	1
3	13	1
4	13	1
5	18	0
6	7	0
7	10	1
8	12	0
9	8	0
10	5	0
TOTALS	<u>103</u>	<u>5</u>

* Because silent herpetic infection
 had probably occurred in many of the
 older children, the true secondary
 attack rate is likely to be higher.

The disease was seen to be infectious, because a similar syndrome occurred in another member of the household within three weeks in five instances. The infectivity was low; by clinical criteria, the secondary attack rate was about 5 per cent. However, some of the older sibs were probably immune because of early inapparent infection, so that the true secondary attack rate is likely to have been higher. The predelection of the disease for young children was again noted (Table 2).

A further instance occurred in which the disease apparently spread from one family to a neighbour. From such evidence, the incubation period appeared to be ten days, but two other families showed second cases three and five months after the first episode.

Other members in two more families developed febrile illnesses of short duration and with no localising features about seven to ten days after the initial case of stomatitis. These facts are summarised in Fig. 12.

The setting in which some of the cases occurred strongly suggested the herpetic nature of the infection. The saga of family S₁, (Fig.12) illustrates this "guilt by association".

Josephine /

Josephine, aged ten years, developed herpes labialis at Christmas 1963. About seven days later her sister Lydia developed an upper respiratory infection which rapidly became a ragingly fierce broncho - pneumonia. Meantime, sister Christine (case No.15) aged eighteen months, developed febrile aphthous stomatitis, while another sister aged four years, ran a two-day fever with no obvious clinical features. A week later still, a three year old brother also ran a fever of short duration without definite clinical features. One child, a five year old boy, remained fit and well throughout. Subsequent examination of his medical record showed that he had been under our care four years previously because of "stomatitis" .

The stomatitis in a child was associated with recent active herpes labialis in another member of the family or in a playmate, in eleven of twenty-eight cases where this point was specially checked. The association is illustrated in Fig.13, which suggests that the mode of transmission may well be kissing.

SUMMARY AND CONCLUSIONS /

Fig. 12

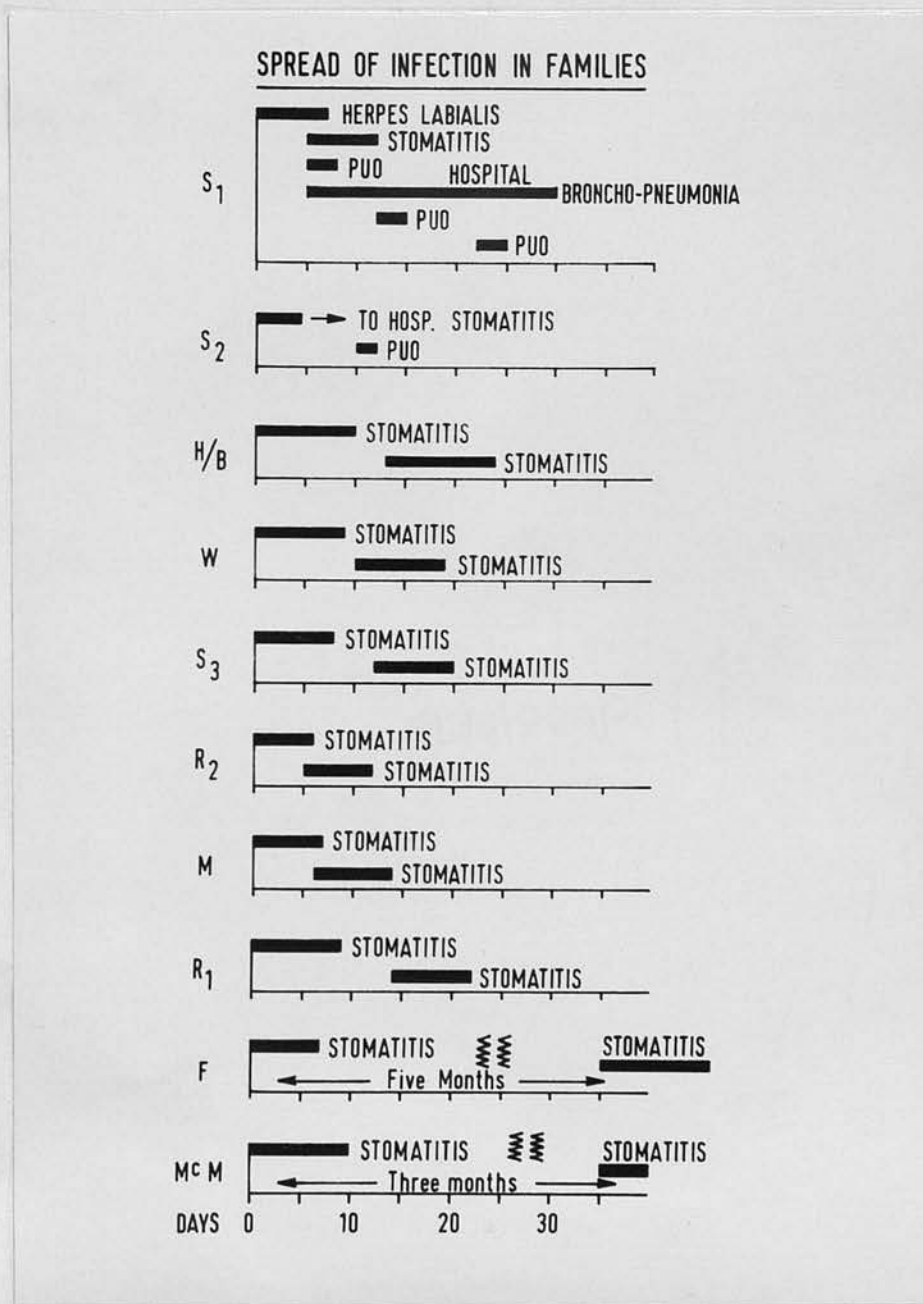


Fig. 13



M.D. Case No.32

Healing herpes labialis on

mother's upper lip left.

Appendix 1A

LABORATORY STUDIES /

SUMMARY AND CONCLUSIONS

Using the simple clinical criteria of mouth ulceration occurring in conjunction with febrile illness, a prospective survey of the patients of one family doctor included fifty children during a period of approximately three years. They all seemed to be suffering from one disease, which was by far the commonest cause of oral lesions in all children seen during the period of the survey. The age distribution of these children showed a marked peak in the second and third years of life. Analysis of the presenting symptoms showed a close association with upper respiratory catarrh. Alimentary symptoms were also common. The oral ulceration was virtually confined to the anterior aspect of the mouth. Various cutaneous manifestations were observed.

All the children were unwell, and some had considerable systemic disturbance. Nevertheless, the disease ran a self-limiting course, with few complications.

The epidemiological and clinical findings strongly implicated herpes simplex virus.

The salient features of the fifty cases are summarised in Appendix 12.

LABORATORY STUDIES

Although the fifty cases of stomatitis were selected by one observer using strict clinical criteria, several diseases of different aetiology might have been included. Because of this, virus isolations, antibody studies and other investigations were attempted.

ANTIBODY STUDIES

VIRUS ISOLATION

Material and Method

During phase 1 of the study an attempt had been made at virus isolation (Case No.4) using ordinary throat swabs and the routine general practitioner specimen collection service. Failure to isolate any virus from the case discouraged further attempts until phase 2. The digital lesion of case No.20 bore such a strong clinical resemblance to "nurse's whitlow" (Stern et al. 1959) that more determined efforts were made at virus isolation. A wooden-shafted swab was used, the tip of which was broken off into a "Bijou bottle" containing Eagle's growth medium. Specimens were then taken personally to the laboratory without delay. The methods employed for virus isolation were those described by Peutherer and Smith (1967).

Results

Herpes simplex virus was isolated from nineteen of twenty-one children /

children. The swabs had been taken from the oral lesions, with one exception (case No.48) : this swab was taken from the throat because of a provisional diagnosis of "pharyngitis" made before the oral lesions had appeared. Virus was isolated also from material taken from two digital lesions, but not from a swab of the nasal secretion of case No.41.

ANTIBODY STUDIES

I was unwilling to subject children at the height of their illness to the additional discomfort of venepuncture. In the one instance where this was done (case No.39) a convincing rise in complement fixing antibody was demonstrated. Antibody, once it has been formed, persists after primary infection (Burnett 1946), although the level may not always remain constant (Buddingh et al. 1953). In order to demonstrate that the children studied had all at least encountered the herpes simplex virus, their antibody levels were estimated at the close of the survey. The results were evaluated against those obtained from children of similar ages and of households of similar size, who had not shown clinical evidence of stomatitis. The opportunity was taken to assess the antibody levels of the mothers of children in index and control groups, and to record the maternal history regarding herpes labialis.

Material and Methods /

Material and Methods

Each index household was matched for numbers and ages (but not sex) of offspring, by selecting the next appropriate household from the practice alphabetical index of families. The register (the "F-Book"), which is used mainly for morbidity recording, is fully described elsewhere (Kuenssberg 1964).

The National Health Service record of every child in all these households was next examined, and the families were visited. If any child in a control family was recorded as having had febrile stomatitis, or if the mother's story was sufficiently suggestive of this illness in any of her children when she was questioned directly on this point, that household was rejected and the next appropriate one was selected. The occurrence of simple aphthous ulceration in a child was not a reason for the exclusion of that family. In all, thirteen households were replaced because a member had suffered from probable herpetic stomatitis.

The composition of a household finally selected as a control occasionally differed from that recorded in the "F-Book": for example, all the children in a family might not be registered with the practice. The large families were not easy to match exactly: the closeness of the matching achieved is illustrated by the fact that the index group contained only three more children under twelve years than the control households. The matching was also tested by parameters not used in the selection of controls; for example/

example, the distribution of children by sex, the differences between matched pairs of households in respect of numbers of children under twelve years, and the number of households where the father was not registered with the practice.

By these criteria the matching was remarkably close (Appendix 7). Where possible, blood was obtained by venepuncture, but in the very young children specimens were occasionally taken by heel-stab.

a) Complement fixing antibodies, 45 matched pairs
 Present in index, absent in controls
 Present in controls, absent in index
 p < 0.01

Both complement-fixing antibody (C.F.) and neutralising titre (N.T.) of the serum were measured by the methods described by Peutherer and Smith (1966:1967).

Results

Antibody levels in children

Neutralising antibodies, in 27 matched pairs
 Present in index, absent in controls
 Present in controls, absent in index
 p < 0.01

Complement-fixing antibody levels were estimated in forty-six index children, all of whom, except two (cases No.25 and No.49), showed the presence of antibody. Of forty-five control children, thirty-two had no antibody. The differences between matched pairs are significant at the 1 per cent level (Table 3a).

N.T. estimations were performed on thirty-one index and thirty-seven control children. The differences between the matched /

Table 4

FLUCTUATIONS IN ANTIBODY LEVELS WITH

Table 3

DURATION OF FOLLOW-UPa) G.P. ANTIBODY

DURATION

Reciprocal of titre	ANTIBODY LEVELS IN CHILDREN	< 1 year	> 1 year
	Number of Cases	Number of Cases	Number of Cases
	DIFFERENCES BETWEEN MATCHED PAIRS		

256

3

0

128

1

0

a) Complement fixing antibodies, 45 matched pairs

Present in index, absent in controls	32
--------------------------------------	----

Present in controls, absent in index	1
--------------------------------------	---

p < 0.01

TOTALS

23

22

b) Neutralising antibodies, in 27 matched pairs

Present in index, absent in controls	19
--------------------------------------	----

b) N.T. ESTIMATIONS

Present in controls, absent in index	0
--------------------------------------	---

DURATION P < 0.01

Reciprocal of titre	< 1 year	> 1 year
	Number of Cases	Number of Cases
> 256	1	6
256	1	7
128	8	3
64	1	0
32	2	1
16	0	0
8	1	0

> 256

1

6

256

1

7

128

8

3

64

1

0

32

2

1

16

0

0

8

1

0

TOTALS

14

17

Table 4

FLUCTUATIONS IN ANTIBODY LEVELS WITH
DURATION OF FOLLOW-UP

a) C.F. ANTIBODY

Reciprocal of titre	DURATION	
	< 1 year Number of Cases	> 1 year Number of Cases
256	3	0
128	1	0
64	3	3
32	6	8
16	3	4
8	1	6
0	1	1
<u>TOTALS</u>	<u>23</u>	<u>22</u>

b) N.T. ESTIMATIONS

Reciprocal of titre	DURATION	
	< 1 year Number of Cases	> 1 year Number of Cases
≥ 256	1	6
256	1	7
128	8	3
64	1	0
32	2	1
16	0	0
8	1	0
<u>TOTALS</u>	<u>14</u>	<u>17</u>

matched pairs parallel the C.F. results, and are also significant at the 1 per cent level (Table 3b).

Certain trends were noted in the fluctuation of C.F. and neutralising titres with the duration of follow-up of the index children. Those who had suffered from stomatitis more than a year previously tended to have a higher N.T. than those whose illness had occurred more recently. (Table 4b). The reverse was true of C.F. antibody levels (Table 4a).

Antibody levels in mothers

C.F. antibody levels were estimated in forty-one mothers of index children. All except one mother had antibody. All except two of forty-one mothers of control children also possessed C.F. antibody. Similar results were also obtained from neutralising titres. The differences between matched pairs are not significant.

Details of the antibody levels in mothers and children are set out in Appendix 13 .

Maternal History of Herpes Labialis

Nineteen of forty-one mothers of index children said they were subject, or had been subject, to recurrent "cold sores".
Fourteen /

fourteen mothers of control children also gave a "positive history". The differences between matched pairs are not significant.

Other Investigations

Five smears from oral lesions were examined for Vincent's organisms and multinucleate cells, with negative results. It is likely that they would have been encountered eventually, but it was considered that persisting with such examinations would not add sufficiently useful information to make the extra swabbing worthwhile.

SUMMARY AND CONCLUSIONS

Herpes simplex virus was isolated from nineteen of twenty-two children swabbed, in the main, consecutively in the latter half of the prospective study. Vincent's organisms and multinucleate cells were not found in the five smears examined for them.

One child who was examined for a rising titre of complement fixing antibody during the acute phase of her illness, showed this phenomenon.

The main laboratory evidence in support of the herpetic nature of the illness is afforded by the antibody studies made at the close of the survey.

Highly /

Highly significant differences were observed between index and control children (matched for age, position in the family and size of household) with regard to complement fixing antibodies and neutralising titres of their sera, supporting the clinical impression of the herpetic nature of the disease.

No difference was noted between mothers of index and control households as regards antibody levels, or history of herpes labialis.

It was noted in passing that children examined within a year of their illness tended to have higher C.F. antibody levels than had children whose stomatitis had occurred more than a year previously. The converse was true of the neutralising titre, so that after a year the antibody response in an affected child resembled that of the adult. It was not possible to study the effect of clinical recurrences on the antibody levels because of the small number of cases.

THE SHORT-TERM FOLLOW-UP

Material and Methods

Possible sequelae fell naturally into three groups, the first of which comprised the recurrent cutaneous lesions. The second group was made up of infections of various kinds. The third group, was composed of recurrent mouth ulcers.

FOLLOW-UP STUDIES /

The /

FOLLOW-UP STUDIES

During my visits to the index and control families for the antibody studies, I observed certain lesions which could be possible sequelae of the original stomatitis, despite the relatively short time elapsing since the primary infection in certain children. Because the occurrence of sequelae has some bearing on the importance of early diagnosis of herpetic stomatitis it seemed worthwhile to consider the nature of the lesions, their frequency and how soon after primary infection they appeared. These questions were examined in two studies. The first was a systematic examination and comparison of the cases from the survey and of children matched for age in the control households selected for the antibody studies - a short-term follow-up. The second study was a retrospective survey of cases of probable herpetic stomatitis, and controls, discovered by a systematic search of certain group practice records.

Present in controls; absent in index

5

0

THE SHORT-TERM FOLLOW-UP

$p < 0.05 > 0.01$

Material and Methods

Possible sequelae fell naturally into three groups, the first of which comprised the recurrent cutaneous lesions. The second group was made up of infections of various kinds. The third group, was composed of recurrent mouth ulcers.

The /

The parents of the 47 control children participating in the antibody studies were asked about these lesions when the blood specimens were being collected, and their National Health Service records were examined for evidence of these conditions, some of which were photographed.

SHORT-TERM FOLLOW-UP

POSSIBLE SEQUELAE

DIFFERENCES BETWEEN FORTY-SEVEN MATCHED PAIRS OF CHILDREN

a) HERPES FACIALIS

Present in index, absent in controls	20
Present in controls, absent in index	3

$p < 0.01$

b) IMPETIGO

Present in index, absent in controls	6
Present in controls, absent in index	5

c) FURTHER MOUTH ULCERATION

Present in index, absent in controls	5
Present in controls, absent in index	0

$p < 0.05 > 0.01$

Herpes labialis had already appeared in a few control children, but the differences between the matched pairs (Table 5a) are significant at the 1 per cent level.

Infections /

The parents of the index and control children participating in the antibody studies were asked about these lesions when the blood specimens were being taken. The children and their National Health Service records were examined for evidence of these conditions, some of which were photographed.

RESULTS

Of the original fifty children entered into the survey, forty-seven were followed-up during the last quarter of 1966. The mean duration of follow-up of the group was approximately fourteen months.

Facial Lesions

Already twenty-one patients had had one or more episodes of lesions on the face. Only seven of these children had been brought to the doctor, an indication that many of the conditions were of a relatively minor nature. Some lesions were the familiar "cold sore" (Fig.14), circumscribed grouped vesicles. Others were less circumscribed, and were occasionally associated with a moist eczematous type of lesion around the eyelids or the nares (Fig.15).

Herpes labialis had already appeared in a few control children, but the differences between the matched pairs (Table 5a) are significant at the 1 per cent level.

Infections /

Fig. 14



D.D. ♀ 4 years Case No. 8

Primary herpetic stomatitis July 1964

Recurrent herpes facialis November 1966

Primary herpetic stomatitis March 1964

Recurrent herpes facialis November 1966

Herpes simplex virus isolated.

Epithelium lesion left nostril.

Fig.15



S.M. ♂ 5 years Case No.2

Primary herpetic stomatitis March 1964

Recurrent herpes facialis November 1966

Herpes simplex virus isolated.

Erythematous lesion left nostril.

Infections

The most obvious infection was impetigo super-imposed on a recurrent local lesion. This is illustrated in Fig.16: in this instance the organism was a β - haemolytic streptococcus.

Another child developed the familiar "cold sore" (Fig.14) which was not clinically impetiginised, but which was followed within three days by impetigo of the R thigh (Fig.17).

Some children were said by their mothers to be more prone to respiratory catarrh than they had been previously: but most of them were growing into the age of the peak prevalence of this group of conditions (Fry 1966). One child (case No.30) suffered from an episode of febrile catarrh three months after having made a complete clinical recovery from the primary stomatitis: the only organism from his throat swab was the herpes simplex virus.

The number of cases with impetigo were too small for valid analysis; such differences as occurred between matched pairs of children are shown in Table 5b.

Mouth ulcers

Seven children gave a history of recurrences of mouth ulceration. One child (case No.22) had an associated fever for which no cause was found. The other six had had one or more episodes of simple ulceration from which they had not suffered previously. This recurrent mouth ulceration was not considered by the parents to be sufficiently serious to "bother the doctor" in /

Fig. 16



G.P. ♀ 3 years Case No.33

Primary herpetic stomatitis December 1965

Impetiginous recurrent herpes facialis in

January 1967.



in five instances. One case of simple ulceration and the child who
has fever and stomatitis was treated by the doctor, but no virus
studies were carried out.

Fig. 17



The
these chil
The d
small for
Blair Cond
No va
diseases b
developed
herpetic
LARI-TRAM
The d

D.D. ♀ 4 years Case No.8
+

Same child as in Fig.14

Crusted impetigo of right buttock and
thigh at the same time as herpes facialis.

in five instances. One case of simple ulceration and the child who had fever and stomatitis were seen by the doctor, but no virus studies were carried out.

Two control children had simple aphthous stomatitis and one of these children had no herpes antibodies in her serum.

The differences between matched pairs shown in Table 5c are too small for valid analysis.

Other Conditions

No very striking difference was noted in the patterns of diseases between the two groups, but one index child (case No.14) developed erythema multiforme sixteen months after her primary herpetic stomatitis.

LONG-TERM FOLLOW-UP

The second study was a retrospective survey of cases of probable herpetic stomatitis, with controls matched for age and sex, against which the possible sequelae noted above might be assessed.

Material and Methods

The National Health Service records of all children born in 1960 and 1959, whose card was filed at one of the two main practice /

practice buildings (Surgery "M") were carefully examined for consultations for "trench mouth", "stomatitis" or "gingivitis". Each case with such a history was then matched for age and sex by pairing it with the next appropriate record without such entries, in the alphabetical file. The age group was deliberately selected because such children would be old enough at the time of follow-up to have met the challenging stimulus of other febrile illness (see Appendix 5) which might activate any latent herpetic infection (Bedson et al. 1961). They would not be so old that any unrecorded stomatitis in the control group would have been forgotten by the parents. All the children were then visited and their parents questioned about their health.

There were records of 357 children born in 1960, and 401 children born in 1959. Most of the children had been with the partnership since birth, although some had joined the list at various ages. The uniformity and quality of the recorded information might vary. As a cross-check on this, the prevalence of some other obvious clinical entity was first calculated in each age group. "Eczema" was selected as a "marker". Among 357 children born in 1960 thirty (8.4 per cent) were recorded as having attended for eczema: thirty-three (8.2 per cent) of the 401 children born in 1959 were noted with this skin condition. The recording was felt to be consistent enough to provide worthwhile information.

Fig. 18

**DISTRIBUTION BY AGE AT PRIMARY ILLNESS
OF 47 CHILDREN BORN IN 1959 & 1960**

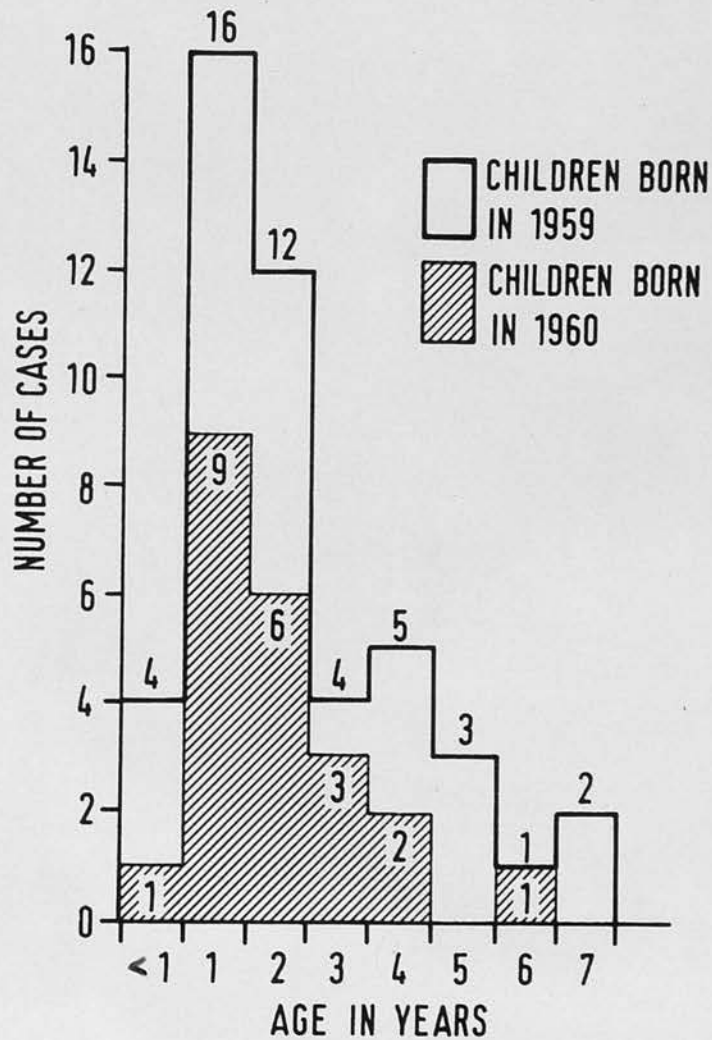


Fig. 19



L.A. ♂ 7 years

"Stomatitis" July 1960

Recurrent herpes labialis November 1966.

Herpes simplex virus isolated from the vesicles.

Twenty-two of the children in Table 6 in 1960 and twenty-five of those born in 1959 had attended with probable herpetic stomatitis.

Some confirmation of the LONG-TERM FOLLOW-UP is provided by the age distribution of the children at the time of their illnesses (Fig. 18)

which is similar to that of the prospective series (Fig. 2).

DIFFERENCES BETWEEN FORTY-TWO MATCHED PAIRS OF CHILDREN

Five of the forty-seven children had already been included in

a) HERPES FACIALIS the prospective study; they were omitted from the retrospective

survey. Present in index, absent in controls 20. The

mean age at onset of the disease was approximately

four years (Appendix 8).

p < 0.01

b) IMPETIGO

Present in index, absent in controls 6

Present in controls, absent in index 5

Twenty-four children gave a history of "cold sores", some of which were evident at the time of examination. The lesions

were more vesicular and circumscribed than those noted in the

previous study (Fig. 19). Among the controls, seven children gave

a history of recurrent facial lesions.

p < 0.05 > 0.01

The differences between the matched pairs are significant at the 1 per cent level. (Table 6a).

Infections

Impetiginous herpes labialis was noted, and one patient was observed with this lesion at follow-up (Fig. 20). Impetigo of various /

Twenty-two of the children born in 1960 and twenty-five of those born in 1959 had attended with probable herpetic stomatitis. Some confirmation of the diagnosis is afforded by the age distribution of the children at the time of their illness (Fig.18) which is similar to that of the prospective series (Fig.2).

Five of the forty-seven children had already been included in the prospective study; they were omitted from the retrospective survey. The results refer to forty-two pairs of children. The mean duration of follow-up of the index group was approximately four years (Appendix 8).

RESULTS

Recurrent Herpes Facialis

Twenty-four children gave a history of "cold sores", some of which were evident at the time of examination. The lesions were more vesicular and circumscribed than those noted in the previous study (Fig.19). Among the controls, seven children gave a history of recurrent facial lesions.

The differences between the matched pairs are significant at the 1 per cent level. (Table 6a).

Infections

Impetiginised herpes labialis was noted, and one patient was observed with this lesion at follow-up (Fig.20). Impetigo of various /

Fig.20



J.H. ♀ 7 years

"Septic throat and mouth ulcer"

May 1960

Impetiginised recurrent herpes

labialis smeared with "Germoline".

September 1966

Fig.21



W.T. ♂ 6 years

"Gingivitis" July 1962.

Seen September 1966 T99.5°F

Herpes simplex virus isolated from
lesions on tongue and lower lip.

Complement -fixing titre 1/32.

various sites was recorded in seven children. Six control children had records of attendances for this condition; the differences between the matched pairs are not statistically significant (Table 6b).

No clear-cut difference was observed between the two groups as regards attendances for respiratory catarrh, but five index children had been referred for tonsillectomy compared with only one control child.

One index child had suffered from an intractable paronychia with the loss of a finger-nail, and another had suffered from very severe recurrent skin sepsis.

Mouth Ulcers

Nine index children had had one or more further episodes of mouth ulceration. Most of the children had not been brought to the doctor. Two were seen, however, because of an associated febrile illness. The child illustrated in Fig. 21, had a two-day's history of malaise. His temperature was 99.5°F , and ulcers were present on the tongue and lips, which were swollen and fissured. Herpes simplex virus was isolated from a swab of the lesions. Only one control child had a history of recurrent mouth ulcers. The differences between the matched pairs (Table 6c) are significant, but only at the 5 per cent level.

Other Conditions /

Other Conditions

Two index children had developed erythema multiforme; sixteen and eighteen months after the clinical primary herpetic infection. Antibody studies on them confirmed that each had at least encountered the herpes simplex virus at some time previously. No controls had suffered from erythema multiforme.

SUMMARY AND CONCLUSIONS

The findings of the two studies are broadly similar, despite the different durations of follow-up. In the first, approximately half of the children who had suffered from herpetic stomatitis developed recurrent facial lesions within fourteen months of their primary illness; the situation had not changed significantly at four years in a second group of children similar to the first.

Super-added bacterial infection was encountered in association with the recurrent lesion, and, although it was not possible to demonstrate this statistically, there was a tendency to sepsis generally in the index children.

There was a trend towards the more frequent occurrence of mouth ulceration following herpetic stomatitis, which was not statistically significant on the numbers available for the short-term follow-up, but which just reached statistical significance in the longer follow-up.

Three children who had had stomatitis were noted to have suffered from erythema multiforme, but no control children had developed the disease.

The functions of the family doctor is to sort out the undifferentiated mass of morbidity which he encounters in his daily work. The common clinical presentations of herpetic stomatitis have been considered in isolation, but how do they appear in the context of general practice?

Factual information was obtained from two studies. In the first, the initial presentation of the disease is viewed against the background of other febrile illnesses of children seen by the family doctor.

Material and Methods

In 1963 the febrile illnesses affecting the children in my day-to-day work were studied in a prospective survey aimed at recording patterns of diagnosis, and the age and sex of the patients, among other things. Every child under twelve years, seen at home or in the consulting room, who had a history of malaise and who was febrile, was included in a study lasting twelve months. It was fortunate that the period chosen was not marked by any major epidemics, although there were two minor outbreaks, one of measles and the other of scarlet.

THE DISEASE IN THE CONTEXT OF GENERAL PRACTICE /

Initial impressions, complications (if any) and final diagnoses were noted, and the information was ultimately transferred to hand-sorting/

THE DISEASE IN THE CONTEXT OF GENERAL PRACTICE

Table 7

One of the main functions of the family doctor is to sort out the undifferentiated mass of morbidity which he encounters in his daily work. The common clinical presentations of herpetic stomatitis have been considered in isolation, but how do they appear in the context of general practice ?

	BOYS	GIRLS	TOTAL
Factual information was obtained from two studies. In the first, the initial presentation of the disease is viewed against the background of other febrile illnesses of children seen by the family doctor.	6	7	13

NO FIRM DIAGNOSIS	36	27	63
<u>Material and Methods</u> PNEUMONIA	41	21	62

In 1963 the febrile illnesses affecting the children in my day-to-day work were studied in a prospective survey aimed at recording patterns of diagnosis, and the age and sex of the patients, among other things. Every child under twelve years, seen at home or in the consulting room, who had a history of malaise and who was febrile, was included in a study lasting twelve months. It was fortunate that the period chosen was not marked by any major epidemics, although there were two minor outbreaks, one of mumps and the other of measles.

Initial impressions, complications (if any) and final diagnoses were noted, and the information was ultimately transferred to hand-sorting/

HERPETIC STOMATITIS
 SEEN AGAINST
 FEBRILE UPPER RESPIRATORY INFECTION (U.R.I.)

Table 7
 NUMBER OF CASES BY AGE

FEBRILE CHILDREN 1963-64

599 EPISODES by DIAGNOSIS

THE FINAL COUNT

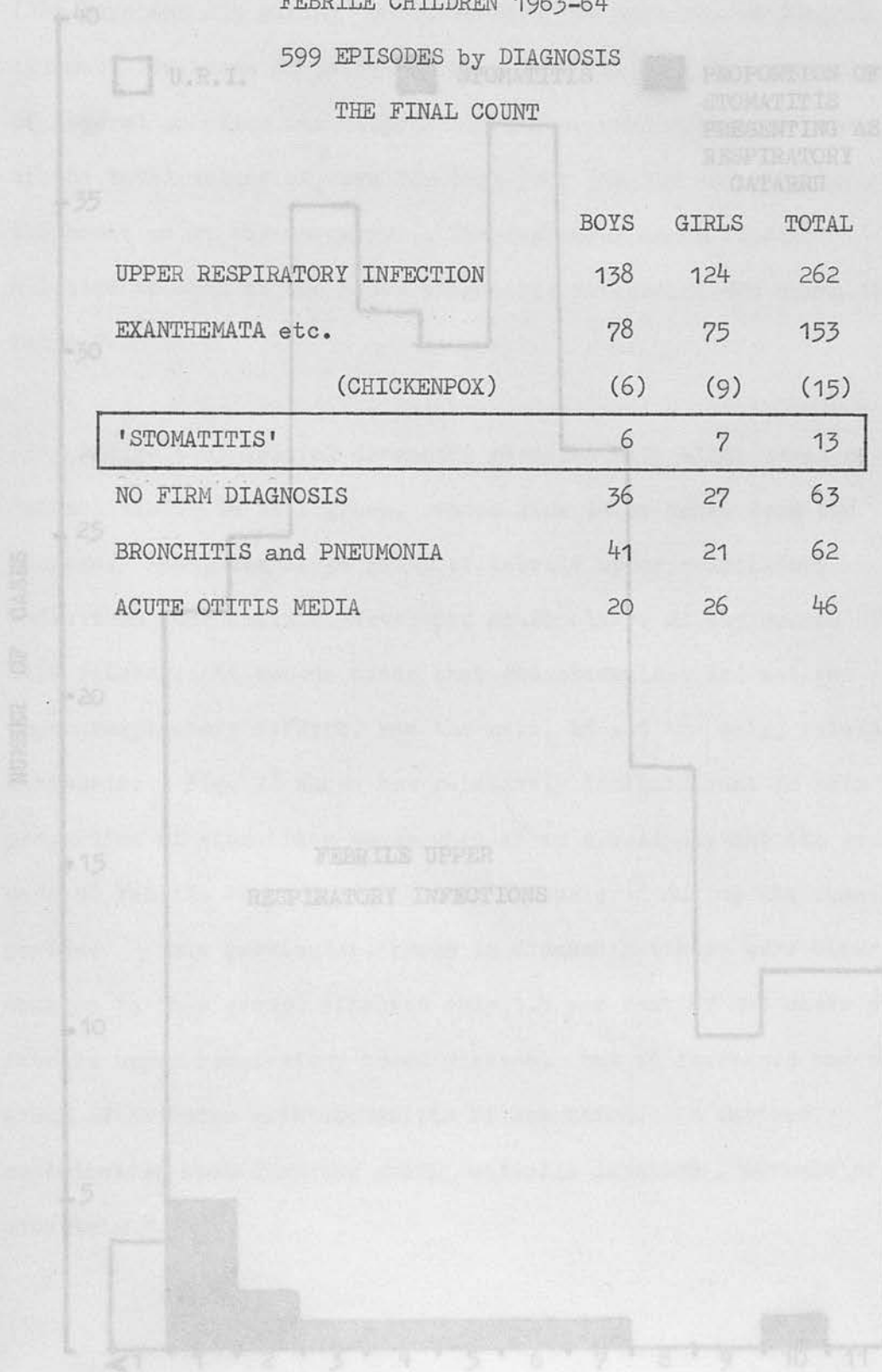


Fig.22

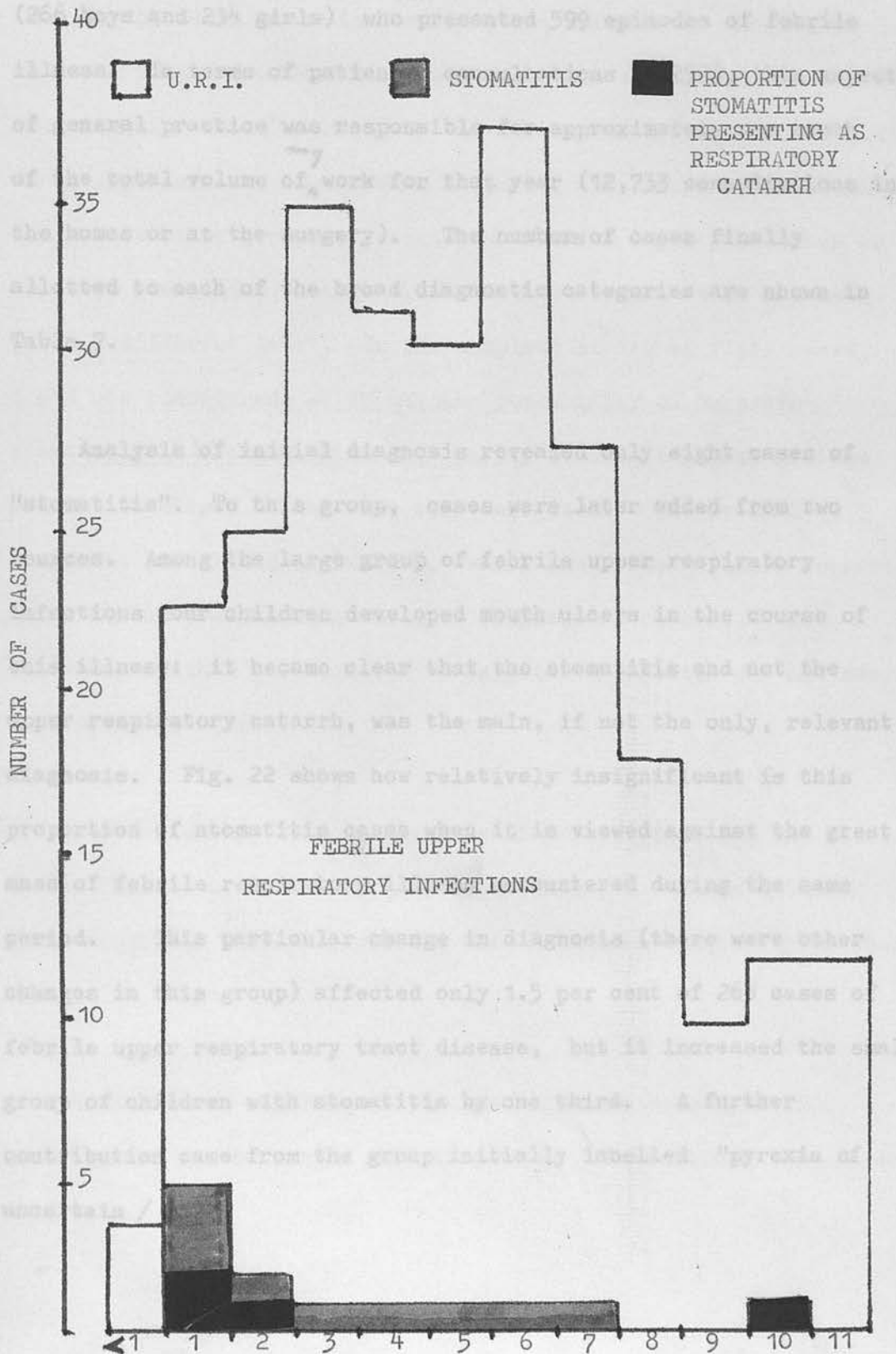
HERPETIC STOMATITIS

SEEN AGAINST

FEBRILE UPPER RESPIRATORY INFECTION (U.R.I.)

ONE YEAR'S EXPERIENCE

NUMBER OF CASES BY AGE



hand-sorting punch cards for analysis. ~~It eventually developed~~
~~mouth ulcers.~~

By these simple criteria, the study included 500 children (266 boys and 234 girls) who presented 599 episodes of febrile illness. In terms of patient - consultations (1,259), this aspect of general practice was responsible for approximately one tenth of the total volume of ^{my} work for that year (12,733 consultations in the homes or at the surgery). The numbers of cases finally allotted to each of the broad diagnostic categories are shown in Table 7. ~~different label. In the complete series of fifty cases,~~
~~I had not considered, at first, the possibility of herpetic~~
~~stom~~ Analysis of initial diagnosis revealed only eight cases of "stomatitis". To this group, cases were later added from two sources. Among the large group of febrile upper respiratory infections four children developed mouth ulcers in the course of this illness: it became clear that the stomatitis and not the upper respiratory catarrh, was the main, if not the only, relevant diagnosis. Fig. 22 shows how relatively insignificant is this proportion of stomatitis cases when it is viewed against the great mass of febrile respiratory illness encountered during the same period. This particular change in diagnosis (there were other changes in this group) affected only 1.5 per cent of 265 cases of febrile upper respiratory tract disease, but it increased the small group of children with stomatitis by one third. A further contribution came from the group initially labelled "pyrexia of uncertain /

uncertain origin" (P.U.O.) when one child eventually developed mouth ulcers.

THE DIAGNOSTIC

In the final analysis for the year, therefore, there were thirteen cases of stomatitis, and not eight as appeared at first. The situation is illustrated by the "truncated pyramids" in Fig. 23. As my experience of the disease deepened, it became apparent that there were other groups of diagnoses in which lay buried cases of herpetic stomatitis, but, initially, at least, they had been given a different label. In the complete series of fifty cases, I had not considered, at first, the possibility of herpetic stomatitis in nineteen children, partly because the oral lesions had not developed at the time they were seen. The initial diagnoses are listed in Table 8, which shows the relative importance of the presentation as upper respiratory catarrh. The frequency of this presentation of herpetic stomatitis did not vary much with age (Table 9).

A relationship between the mode of presentation and the place of the initial contact is suggested in Table 10: those children whose diagnosis was least obvious were seen more frequently in their homes.

Some factors relating to the home circumstances were then investigated in the second two studies. The clinical impression was/

Fig.23

THE DIAGNOSTIC
SITUATION
FEBRILE ILLNESS IN CHILDREN

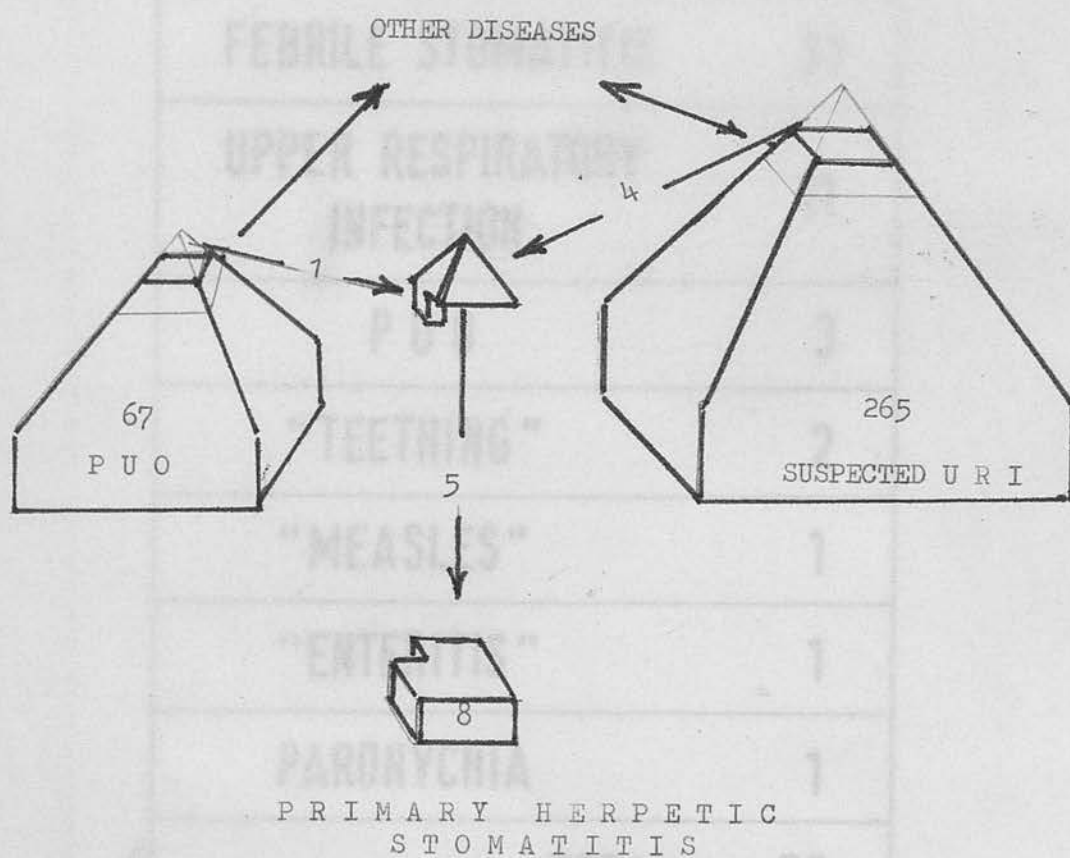


Table 8

**PRIMARY H. SIMPLEX
50 CASES
INITIAL DIAGNOSES**

FEBRILE STOMATITIS	31
UPPER RESPIRATORY INFECTION	11
P U O	3
"TEETHING"	2
"MEASLES"	1
"ENTERITIS"	1
PARONYCHIA	1
TOTAL	50

Table 9

INITIAL DIAGNOSIS

HERPETIC STOMATITIS 50 CASES

HERPETIC STOMATITIS

PRESENTATION AND PLACE OF CONSULTATION

Presentation as Upper Respiratory Infection (U.R.I.)

and age of patients.

	CONSULTATION AT		TOTAL
	HOSPITAL	HOME	
Mouth ulceration		Children under 3 yrs. 6	Children 3 yrs. and over
? U.R.I.	6	7	13
ALL OTHER	31	<u>25</u>	<u>14</u>
TOTAL		<u>32</u>	<u>18</u>

was that the households of affected children tended to be larger than the average. The hygienic standards of housing generally seemed poorer. Miller *et al.* (1960) had found a positive statistical correlation between the occurrence of herpetic stomatitis and the presence of a dog in the household: was this true of my series?

INITIAL DIAGNOSIS
HERPETIC STOMATITIS 50 CASES

PRESENTATION AND PLACE OF CONSULTATION

Material and Methods

	CONSULTATION AT		
	SURGERY	HOME	TOTAL
Mouth ulceration	25	6	31
Other	6	13	19
	31	19	50

The questions of household hygiene, housing and household pets were examined in the forty-one pairs of households used for the antibody studies (page 38). The standard of hygiene was assessed by the smell of the house, the general state of cleanliness and by the presence of soap in the bathrooms.

Results

The distribution of the households by the numbers of children is shown in Table 11. Comparison between the two groups confirms the clinical impression that the disease was seen in larger households than usual.

was that the households of affected children tended to be larger than the average. The hygiene and standards of housing generally seemed poorer. Miller et al. (1960) had found a positive statistical correlation between the occurrence of herpetic stomatitis and the presence of a dog in the household: was this true of my series ?

Material and Methods

In all forty-four households of affected children, the numbers of children under twelve years of age were compared with the sizes of forty-four households with children attending my surgery. These households were taken at random from the "F. Book". (Kuenssberg 1964).

The questions of household hygiene, housing and household pets were examined in the forty-one pairs of households used for the antibody studies (page 38). The standard of hygiene was assessed by the smell of the house, the general state of cleanliness and by the presence of soap in the bathroom.

Results

The distribution of the households by the numbers of children is shown in Table 11. Comparison between the two groups confirms the clinical impression that the disease was seen in larger households than usual.

The /

The type of housing was remarkably similar in the two groups, being mainly new Corporation (Appendix 9). The group of families affected by the disease contained the two worst houses, and the control group the two best (Table 12).

COMPARISON OF HOUSEHOLD SIZES

44 INDEX HOUSEHOLDS and 44 RANDOM HOUSEHOLDS
WITH CHILDREN WHO NORMALLY ATTEND MY SURGERY

Composition	INDEX		RANDOM	
	Number of Households	Number of Children	Number of Households	Number of Children
1 child	2	2	13	13
2 children	11	22	20	40
3 "	13	39	5	15
4 "	6	24	3	12
5 "	3	15	2	10
6 "	8	48	1	6
7 "	0	0	0	0
8 "	1	8	0	0
TOTALS	44	158	44	96

The type of housing was remarkably similar in the two groups, being mainly new Corporation property (Appendix 9). The group of families affected by the disease contained the two worst houses, and the control households showed the three best (Table 12).

In most of the matched households (thirty-two of forty-one) there were corresponding degrees of hygiene, which was mainly good. However, in eight of the nine "unlike pairs" the household hygiene was poorer in those families in whom herpetic stomatitis had occurred (Table 12).

The tenancy regulations for Corporation houses, and the many new multi-storey flats did not encourage families to keep pets. There were no obvious differences between the two groups in the overall pattern of such pets as were kept. The differences between matched pairs of households in respect of the presence of a dog in the house are not statistically significant (Table 12).

a) A DOG IN THE HOUSE

Present in index, absent in control 7)

Absent in index, present in control 7)

HERPETIC STOMATITIS IN HOSPITAL PRACTICE /

HERPETIC STOMATITIS IN HOSPITAL PRACTICE

Table 12

Although this thesis is primarily concerned with the disease in general practice, a short study of the hospital physician's view of the situation is included to provide both a sense of perspective and objective information on possible diagnostic difficulties encountered by other family doctors in the region.

a) <u>TYPE OF HOUSING</u>	<u>INDEX</u>	<u>CONTROL</u>
New flats and "Maisonettes" (5 yrs.old)	27	20
Older flats (up to 30 years old)	10	18
Privately owned house	0	3
Prefabs	2	0
Slum property	2	0
b) <u>HOUSEHOLD HYGIENE</u>		
<u>Material and Methods</u>		
Good in index, poor in control	1))
Poor in index, good in control	8))
	$p < 0.05$	> 0.01
c) <u>A DOG IN THE HOUSE</u>		
Present in index, absent in control	7))
Absent in index, present in control	7))

ResultsHERPETIC STOMATITIS IN HOSPITAL PRACTICE

Although this thesis is primarily concerned with the disease in general practice, a short study of the hospital physician's view of the situation is included to provide both a sense of perspective and objective information on possible diagnostic difficulties encountered by other family doctors in the region.

The clinical presentations of herpetic stomatitis, despite their differences, usually suggest an infectious "fever" of some sort, even when the diagnosis is obscure. The infectious diseases hospital was this one obvious source of objective information for this study.

Material and Methods

By courtesy of the physician superintendant, information on all children in the Edinburgh City Hospital with a final diagnosis of herpetic stomatitis during the three years of my general practice survey was made available to me. It was particularly fortunate that a virus laboratory service had been set up within the hospital shortly before, and interest in virus diseases had been stimulated thereby. As a cross-check on the clinical material, therefore, information was sought from the laboratory on all cases on whom herpes simplex studies had been made during this period.

Results /

Results

During the period of approximately three years only twenty-nine cases of possible herpetic stomatitis were admitted to the Edinburgh City Hospital. The clinical diagnosis was supported by virological studies in fourteen instances. The age distribution of this small group shows the characteristic peak in the second and third years of life (Appendix 10). All the children were, of course, ill, but the systemic disturbance was more marked than it was in the general practitioner series - one child had a temperature of 104.8°F; two children had splenomegaly. Adverse social circumstances were additional reasons for requesting admission of seven children.

The digital lesion was a troublesome feature in one case.

The variety of provisional diagnoses on admission is shown in Table 13, from which it will be seen that only one child was admitted with the diagnosis of primary herpetic stomatitis.

Details of the cases are set out in Appendix 10.

SUMMARY AND CONCLUSIONS/

SUMMARY Table 13 DISCUSSIONS

Herpetic stomatitis was observed in the routine of busy general practice against the background of HERPETIC STOMATITIS illnesses in children in

a prospective study lasting one year. Just under one half of 599 illnesses were febrile upper respiratory catarrh, which made the

EDINBURGH CITY HOSPITAL

November 1963 - September 1966

diagnosis of the early catarrhal phase of herpetic stomatitis much more difficult. Other atypical presentations of the disease were

PROVISIONAL ADMISSION DIAGNOSIS IN 14 CASES

lost among various common general practice labels of convenience such as "P.U.O." and "Teething".

SUSPECTED DIAGNOSIS

Number of Cases

Trench mouth or "stomatitis"	4
Tonsillitis	3
Measles	1
Meningitis	1
Impetigo of face	1
Gastro-enteritis	1
Glandular fever	1
Pyrexia of uncertain origin	1
Herpetic stomatitis	1

14

The strikingly different frequency, mode of presentation, and severity of the disease seen in one hospital were noted.

SUMMARY AND CONCLUSIONS

Herpetic stomatitis was observed in the routine of busy general practice against the background of febrile illnesses in children in a prospective study lasting one year. Just under one half of 599 illnesses were febrile upper respiratory catarrh, which made the diagnosis of the early catarrhal phase of herpetic stomatitis much more difficult. Other atypical presentations of the disease were lost among various common general practice labels of convenience such as "P.U.O." and "Teething".

The diagnosis had sometimes to be made in circumstances more adverse than usual, in homes of low standards of hygiene, among households crammed with children housed in poorer buildings.

Evidence from the infectious diseases hospital showed that diagnostic difficulties were shared by other family doctors. The strikingly different frequency, mode of presentation, and severity of the disease seen in one hospital were noted.

DISCUSSION //

Marked constitutional DISCUSSION understandably a feature of the literature, because this is one of the main reasons why patients THE NATURE OF THE ILLNESS STUDIED children in the present series

The consistent clinical picture of the children in the main survey suggested that they were suffering from one disease. The clinical similarity between this series and accounts such as those of Scott (1954) and Brain (1956) strongly suggested that the disease was herpetic in nature. The age distribution, for example, is regarded by Miller et al. (1963) as characteristic of herpetic stomatitis. Indeed, these authors came to regard all febrile stomatitis in children between the ages of ten months and five years as herpetic, a view echoed by Hansen (1961). The equal sex distribution agreed with the observations of Reade (1961) and Hansen (1961). The significantly poorer hygiene in affected families, noted in the present series, is constantly reiterated in all the clinical reports. However, the differences in hygiene and housing between index and control households of the present series were not as marked as the literature would suggest. Increasing affluence in recent years may have altered the situation since Burnet and Williams (1939) drew attention to this point. Furthermore, because most of the previous studies have been based on "dispensary practice" or orphanage populations, it is probable that too much has been made of the adverse social factors, important as they are.

Marked /

Marked constitutional upset is understandably a feature of the literature, because this is one of the main reasons why patients are referred to hospital. All the children in the present series were ill (pyrexia being one of the criteria of admission to the study), but the patients were not as disturbed as those admitted to the Edinburgh City Hospital. These different grades of severity suggest the possibility that there exist mild forms of the disease insufficiently severe to prompt the parents to call for medical help. Hale et al. (1963) observed three of their thirteen orphanage children to be affected so slightly that they might easily have escaped detection in a non-institutional environment. Such an observation indicates the need for caution in comparing epidemiological data obtained from different sources. The parental anxiety, which was such a prominent feature in some cases, and which was partly responsible for the initial call for help, is specially mentioned by Court (1963).

Of the complications, the digital lesions were noted more frequently in the present study (seven of fifty children); for example they were observed only in two of eighty-eight cases in one of the original accounts (Dodd et al. 1938) and in only one of the twenty-one children in the series of Scott et al. (1941). The presence of the digital lesion may confuse the diagnosis by raising the possibility of "hand foot and mouth" disease (see page 95).

There /

There were no serious complications, such as severe dehydration (Scott et al. 1941), haemolytic anaemia (Todd and O'Donohoe 1958) or encephalitis (Smith et al. 1941). The disease followed the relatively benign self-limiting course observed by most authors, but it is a potentially fatal condition, as Celsus observed. Hansen (1961) and Carter (1961) recorded numerous deaths in their series. It is true that their children were retarded or malnourished - circumstances which favour the generalised spread of the virus (Becker et al. 1963).

There are other clinical phenomena supporting the herpetic nature of the stomatitis in this series, features more obvious to the family doctor than to his hospital colleagues. Active herpes labialis in the family at the time of the child's illness, and the high proportion of children who subsequently developed herpes facialis are examples of this circumstantial evidence.

The clinical picture of herpetic stomatitis is a florid one (MacGregor 1960); so much so, that Brimblecombe (1955) states that virus isolation and complement-fixing antibody tests are unnecessary for routine diagnosis. The ideal of supporting the clinical evidence with laboratory tests discussed by Reade (1961) is possible only in hospital, although this study went some way towards fulfilling such criteria. Despite the delays in transporting specimens from general practice to the laboratory, a high proportion /

proportion of virus isolations was achieved (nineteen of twenty-two lesions swabbed). The one child (case No.39) examined for a rising titre of complement-fixing antibodies during the acute phase demonstrated the phenomenon convincingly. Forty-four of the forty-six children tested had antibodies (some of high titre) to the herpes simplex virus at follow-up examination. It is possible that the two children (cases No. 25 and No.49) failing to show antibodies had not, in fact, suffered from herpetic stomatitis. On the other hand, they may have been examined at a time when the antibody response had waned, during a "trough", such as has been postulated by Yoshino et al.(1962). Halonen (1955) failed to demonstrate antibodies in eight of fourteen cases examined later than two weeks after the primary illness. The contrast between the proportion of children showing antibodies in index and control group is striking. In the light of this clinical, epidemiological, and virological evidence, it is reasonable to conclude that the stomatitis with which this thesis is concerned is herpetic in nature. The disease was not a rarity.

INCIDENCE AND PREVALENCE

Allowing for the turn-over of patients in the practice population, the incidence was approximately 5.0 per thousand persons on the list per year. This is higher than the figure quoted by Hodgkin (1966) who found an incidence of 2.1 per thousand per year in his general practice. The difference may be due, in part, to the large proportion of children in the setting of the present study, and /

and to the increased likelihood in a large group practice of one doctor seeing another's patients. It is to be regretted that a further potential source of information on incidence of the disease - the painstaking study on morbidity in general practice (Logan and Cushion 1958) - should prove unhelpful. The necessary data are buried in statistics scattered under different headings, and are impossible to collate.

Information on prevalence in the present study comes from three sources. In the group of 357 children born in 1960, the prevalence was 6.1 per cent. Among the 401 children born in 1959, it was 6.2 per cent. These figures are likely to be an under-estimate, and this is borne out by the prevalence of 9.0 per cent in the 145 children of households originally matched for control purposes. Miller et al. (1963) found 114 of 847 children were affected in their first five years, a cumulated prevalence of 13.5 per cent.

The disease is not encountered to the same extent in well-to-do communities: for example, it formed an insignificant fraction (possibly only fifty-nine of 25,000 illnesses) of the morbidity reported in the Cleveland study (Dingle et al. 1964) in which most families were of superior social status.

A study of statistics from hospital series shows a sharp contrast to those from general practice. During the period of /

of this survey, only twenty-nine cases were admitted to the Edinburgh City Hospital which serves a population of perhaps half a million. In Glasgow, a firm diagnosis based on virological evidence was made in forty-three cases in the Regional Virus Laboratory, Ruchill Hospital over a four year period (Duncan and Ross 1966). In the course of one year, during which 5000 children under five years were seen in the out-patient department of an American hospital, Scott (1954) found thirty-eight cases. These figures underline the fact that the disease is more frequently seen in general practice than in hospital. It is as common as the more severe forms of chickenpox (Table 7) or as mumps or rubella (Miller et al. 1963).

THE RESPIRATORY CATARRHAL PHASE

Perhaps the most significant difference between the present series and previous accounts was the prominence of upper respiratory catarrh exhibited by all the children, in a quarter of whom it was the presenting feature. Respiratory symptoms are sometimes mentioned as an incidental feature. Thus, Scott et al. (1941) state that upper respiratory infection "co-occurred with" the onset of the stomatitis in five of their series of twenty-one patients. In certain text-book accounts, too, the respiratory catarrh, overshadowed by the obvious stomatitis, is regarded as a separate phenomenon predisposing to the herpetic infection: the analogy to the association of respiratory infections with recurrent herpes labialis is clear. However, the regularity with which this feature appeared in the present study suggests a closer relationship.

Buddingh et al. (1953) refer to a co-incidental "tracheitis and bronchitis which may be herpetic in origin". Swabs for bacteriological and virus examination were taken from case No.48 on the second day of his illness, which was diagnosed "acute pharyngitis" before oral ulceration had developed. Herpes simplex virus was the only significant agent isolated. There is thus the possibility that the upper respiratory catarrh is an integral part of the illness in its early stage. This concept is in line with the growing recognition of the role of the virus in respiratory infections generally (Evans and Dick 1964: Monthly Bull. Minist. Health 1964). Whatever the interpretation of the finding, the early respiratory catarrhal phase is significant in a discussion of the diagnosis in general practice.

THE DIAGNOSIS IN GENERAL PRACTICE

Even although herpetic infection might be the commonest cause of febrile stomatitis, and even if the clinical picture is so clear-cut as to render unnecessary laboratory confirmation, the findings of the present studies show that problems in diagnosis do arise at two different levels. The first concerns the differential diagnosis of the individual case.

Although the characteristic lesion is the oral ulceration, and earlier, features, such as malaise, pyrexia and respiratory catarrh, frequently (one in three cases) cause parents to seek medical help. These other features are common to many different conditions /

conditions seen in general practice; conditions which occur more frequently. Early cases of herpetic stomatitis, interpreted in terms of "probability diagnosis", are easily mis-labelled. Confusion with febrile upper-respiratory infection readily occurs. This mode of presentation of stomatitis is as frequent in the young as in the older children (Table 9). On the other hand, as Fry (1966) points out, febrile upper respiratory infection occurs less frequently in the first three years of life (see also Fig.22). Herpetic stomatitis thus assumes a greater importance in the differential diagnosis of febrile upper respiratory catarrh in the young child.

If the diagnosis is not considered at the outset, the subsequent development of oral ulceration tends to be regarded as "a complication", and the impact of the condition on the family doctor is thus cushioned. Again, however disreputable the diagnosis of "teething" may have become, it is difficult to differentiate the early phase of herpetic stomatitis from disturbance common at this time. The quotation at the frontispiece, culled from the section on teething in *La Paedotrophia* (Sainte-Marthe 1584), was chosen partly to illustrate this difficulty. On the other hand the young child may not complain of a sore mouth in the early stages of the disease. If systemic disturbance is severe and meningism present, the distinction from acute meningitis is not easy. Should the lymphadenopathy be marked, glandular fever becomes a likely diagnosis. The resemblance may be more than superficial: Parsons (1940) /

(1940) recorded an absolute and relative monocytosis in many instances in his series of 115 children with various types of stomatitis some of which were undoubtedly herpetic in nature. Case No.1 of the City Hospital series (Appendix 10) showed atypical mononuclears in his blood.

The diagnosis of the individual case is obscured not only by the atypical features, but also by other factors peculiar to general practice. The adverse circumstances under which an initial diagnosis may have to be attempted in the home have already been mentioned. Diagnosis in general practice must often be influenced by probabilities (Hodgkin 1966); during an episode of measles, for example, it is possible to be reasonably certain about a case of measles seen in the catarrhal phase, even in the absence of Koplik's spots. Herpetic stomatitis, except in unusual circumstances (Levine et al. 1939, Hale et al. 1963), does not occur in epidemics. The family doctor is thereby deprived of a stimulus to the raising of his "index of suspicion".

The second level at which the problem of diagnosis may be considered is the general lack of awareness of herpetic stomatitis as a clinical entity. In addition to my own personal experience of the disease, and discussion with colleagues in general and paediatric practice, there is evidence in the pattern of admission diagnosis in the Edinburgh City Hospital series (Table 13). This pattern resembles that of a larger series from Glasgow, set out in Appendix /

Appendix 11 (Duncan and Ross 1966) : only three of their forty-three cases were admitted with a firm diagnosis of herpetic stomatitis. Hope-Simpson (1964) discussing herpes simplex in the "Encyclopaedia of General Practice" states : " The primary infection cannot be clinically differentiated from the other acute febrile illnesses of infancy".

This failure to recognise the condition is mentioned by several authors (Frankl 1960, MacGregor 1960, Reade 1961). If such an important "pigeon-hole" is missing from the "sorting office", it is small wonder that the "mail is misdirected". "Trench mouth" then becomes the main alternative diagnosis. If this term is employed with its connotation of an ulcerative necrotising affection of the mouth and gums (Smitt 1965) this alternative does not fit the clinical picture: but the situation is obscured by the fact that Vincent's organisms may be isolated from a wide range of oral conditions (Lichtenberg et al. 1933) including, on occasion, herpetic stomatitis (Dodd et al. 1938).

ORIGINS OF THE LACK OF AWARENESS

The disease has been described only comparatively recently, and, as a result, it has yet to be accorded its due place in some undergraduate text-books. For example, Sheldon (1962) in a short section on "stomatitis", writes "The virus of herpes simplex is sometimes the causative agent". Undergraduate teaching is still conditioned by hospital morbidity, and the relatively small numbers of /

of herpetic stomatitis seen in hospital are bound to give a false impression of its incidence and importance in the community. At the post-graduate level, the impact of the disease on the family doctor is lessened by the factors discussed above.

DIFFERENTIAL DIAGNOSIS

If a child suffering from herpetic stomatitis presents with oral lesions already developed and if the family doctor is aware of the existence of the clinical entity, the differentiation from the long list of possible conditions (Table 14) is straightforward. Vincent's angina, whatever its aetiology may be, differs in several respects from the herpetic stomatitis seen in this series. Vincent (1899) described two kinds of "angina" - a "diphtheria-like" form, and a commoner type associated with deep ulceration: "Je n'ai, personnellement, observé cette affection que chez l'adulte", he further states. The contrast between Vincent's angina and herpetic stomatitis is fully described by Frankl (1960).

While the lesion of simple recurrent aphthae (Fig.24) can be indistinguishable clinically from the formed ulcer of herpetic stomatitis, the absence of systemic upset, the history of previous episodes of aphthae and the failure to isolate virus from the lesion, which does not have an initial vesicular stage, all help in the differential diagnosis.

Thrush/

Table 14

PRIMARY HERPETIC STOMATITIS

DIFFERENTIAL DIAGNOSIS

a) Constitutional upset and respiratory catarrh

Respiratory diseases: influenza, pneumonia, etc.
 Prodromal measles
 Glandular fever
 Other causes of "P.U.O." in children: acute
 pyelonephritis, meningitis

b) Local condition

"Teething"
 Thrush
 "Trench mouth" (Vincent's angina)
 Recurrent aphthous ulcer
 Herpangina
 "Hand, foot and mouth" disease
 Chickenpox
 Catarrhal stomatitis
 Measles
 Agranulocytosis, leukaemia and other blood dyscrasias
 Localised erythema multiforme
 Avitaminosis
 Side effects from certain anticonvulsants
 Poisoning with heavy metals

c) Other features

Pyogenic paronychia
 Acute gastro-enteritis, bacillary dysentery, acute
 appendicitis, acute non-specific mesenteric adenitis
 Rubella, morbilli, scarlet fever

Fig. 24



P.M. ♀ 8 years

Maximal surface lower lip shown

J.K. ♀ 4 years

Aphthous ulcer buccal aspect
 left cheek. Second episode.
 Herpes simplex virus not isolated.
 No systemic upset. C.F. antibody
 to herpes virus was not present.

Fig. 25



P.W. ♀ 8 years

Mucosal surface lower lip shows
oral lesion of chickenpox.
Facial vesicles also present.

Thrush, with its raised adherent white patches in the young baby, does not pose a serious differential diagnostic problem, and its presence in the list of hospital admission diagnoses (Appendix 11) probably indicates the lack of a suitable alternative label on the part of the doctor.

The entity recently described as "hand, foot and mouth disease" (Alsop et al. 1960), a syndrome associated with Coxsackie A-16 virus, is not associated with prodromata, and runs a milder course. Vesicles or bullae appear on hands, feet and occasionally buttocks, and the stomatitis is not associated with facial lesions. There may be a form in which the oral lesions are confined to the median raphe of the hard palate and the fraenum of the tongue (Meadow 1965). The development, in the course of herpetic stomatitis, of a digital lesion may cause confusion, and virological studies may be required to settle the problem.

Another syndrome associated with ulceration of the oropharynx, and also with Coxsackie virus (but with serotypes A 2, 5, 7, and 10), is herpangina (Zahorsky 1924; Lerner et al. 1963). The lesions usually are restricted to the back of the pharynx.

A more common condition, bearing a superficial resemblance to herpetic stomatitis, is chickenpox (Fig. 25) but the oral lesions are more erythematous, and the vesicles on the trunk and elsewhere together with evidence of high infectivity make the diagnosis clear.

The existence of catarrhal stomatitis as a separate entity has been questioned (Scott et al. 1941: Ellis and Mitchell 1965): catarrhal, aphthous, and ulcerative stomatitis may be simply different names indicating progressive severity of the same condition, many instances being caused by herpes virus. The infant sister of case No.50 was seen one week before her brother's typical primary herpetic stomatitis. She appeared to have a catarrhal stomatitis, without much systemic upset and without oral ulceration. In retrospect, she may have had primary herpetic stomatitis. The remainder of the diagnoses in Table 14 will usually become obvious from the context in which they occur, but the question of measles and stomatitis requires fuller discussion.

MEASLES AND STOMATITIS

Case No.46 of the present series, a boy aged one year, developed stomatitis seven days after the onset of a mild attack of measles. Herpes virus was isolated from the mouth ulcers, and at follow-up four months later antibodies to the herpes virus were present. It is likely that he suffered from two diseases; Karlitz (1962) states that herpetic stomatitis is a fairly frequent complication of measles, although this is not my experience. In view of the transient generalised rashes exhibited by Case No.47 of the general practice series and case No.9 of the City Hospital series, the morbilliform rash might have been part of the stomatitis.

The /

The situation is complicated by the occasional development of non-herpetic oral ulcerations as part of the clinical picture of measles.

In a boy aged two years (Fig. 26) developed painful swollen cracked lips and a generalized oral catarrh in the course of severe measles in January 1967. Small ulcers appeared on the tongue, from which no

Fig. 26



Measles Stomatitis

factor would thereby suggest penicillin to be effective: this is misleading, and therefore misleading the patient to the antibiotic. Furthermore, it fails to alert the physician to the possibility of serious complications developing. But the main objection to loose terminology is the lessening of one's appreciation of the significance of the herpes simplex virus as a pathogen. Stomatitis is one of several clinical manifestations resulting from primary infection (Secti *et al.* 1952) - other diseases are listed in /

The situation is complicated by the occasional development of non-herpetic oral ulceration as part of the clinical picture of the measles.

L.M. a boy aged two years (Fig.26) developed painful swollen cracked lips and a generalised oral catarrh in the course of severe measles in January 1967. Two small ulcers appeared on the tongue, from which no herpes virus was isolated; his serum contained antibodies to herpes but the pattern did not suggest a recent primary infection: antibodies to measles were demonstrated. Scott et al. (1941) record a similar case.

THE SIGNIFICANCE OF MAKING A TRUE DIAGNOSIS

Since herpetic stomatitis is usually a mild, self-limiting condition, does it matter what label is used? Why not continue to call it "trench mouth"? Apart from an academic objection, the implication that Vincent's organisms are the significant aetiological factor would thereby suggest penicillin to be effective: this is misleading, and there is the risk of sensitising the patient to the antibiotic. Furthermore, it fails to alert the physician to the possibility of serious complications developing. But the main objection to loose terminology is the lessening of one's appreciation of the significance of the herpes simplex virus as a pathogen.

Stomatitis is one of several clinical manifestations resulting from primary infection (Scott et al. 1952) - other diseases are listed in /

in Table 15. The fact that the control children, selected by the exclusion of stomatitis alone, lacked antibody as often as they did confirms this condition in its important place in the list of diseases resulting from infection. On the other hand, the relatively small proportion of control children who had developed antibodies shows that inapparent infection in childhood was not as common in this study as in earlier reports. Scott (1954) estimates that clinical symptoms developed in only 1.3 per cent of infected children under 5 years of age. In the present study, some twelve children were seen each year with the clinical disease from among approximately 400 children under five years of age. Assuming 60 per cent had encountered the virus - and recent figures from Edinburgh suggest that 40 per cent is a more realistic estimate (Peutherer and Smith 1967) - the proportion of children showing symptoms is four times Scott's estimate. It is likely that overt disease results more frequently than has been thought: the illnesses, however, are so mild that they never reach hospital. Only one of the fifty children in the prospective study was admitted to hospital.

Failure to accord stomatitis its proper title further diminishes the significance of herpetic infection by obscuring the link with sequelae.

SEQUELAE /

Table 15

DISEASE STATES CAUSED BY HERPES SIMPLEX VIRUS

PRIMARY INFECTIONS

1. Acute gingivo-stomatitis
2. Conjunctivitis
3. Primary kerato-conjunctivitis
4. "Nurse's whitlow"
5. Vulvo-vaginitis
6. Eczema herpeticum
7. Meningo - encephalitis
8. Herpes neonatorum

SEQUELAE

The natural history of herpetic infection is summarised in Table 16. Once the infection has occurred, the virus appears to live in the cells of the host - though exactly where is a matter of controversy. "There is no evidence", states Burnet (1946), "that it is ever eliminated", and he underlines the uniqueness of an organism capable of infecting about 90 per cent of its possible hosts for about 90 per cent of their lives. The evidence for continued survival of the virus is partly serological, and it is not clear from the literature what proportion of patients who have suffered from stomatitis develop further clinical evidence of herpetic morbidity. There is some doubt, too, as to the morbidity to be ascribed to recurrent herpes simplex infection.

The least controversial issue is herpes labialis, which affected approximately half the children in the present study within two years of the primary infection. It is possible that the primary stomatitis merely accelerated a process which is inevitable, because most of the population eventually become infected by the virus. The present studies were not designed to answer this question, but the high prevalence of herpes labialis among mothers of control households (fourteen of forty-one) suggests that this is so: however, in the absence of a full previous herpetic history from these mothers a firm conclusion cannot be drawn. Even if stomatitis merely hastens the onset of recurrent /

Table 16

THE NATURAL HISTORY OF HERPES SIMPLEX

(SCOTT 1954)

Susceptible host + virus = primary infection
 (no circulating antibodies)

Primary infection = a) manifest disease = local lesion +
 systemic illness
 b) subclinical infection = no visible
 disease

Recovery = carrier state (circulating antibodies)

Carrier state = a) recurrent disease = local lesion
 usually without systemic illness
 b) latent infection = no visible illness

Carrier state \rightarrow virus \rightarrow infection of susceptible host

recurrent herpes labialis, the morbidity is all the greater because it occurs in childhood (Fig.27) and is so often associated with secondary impetigo. The tendency to sepsis and respiratory catarrh, however, is more likely to be an expression of other factors, such as growing up in larger families with poorer hygiene, rather than a direct result of herpetic infection.

More controversial is the interpretation of subsequent episodes of oral ulceration. The obvious explanation, that they are herpetic in nature, is supported by the findings in case W.T. (Fig.21) who apparently suffered from a clinical recurrence of febrile stomatitis four years after his primary episode, and from whom herpes virus was isolated. However, as Dudgeon (1950) points out, isolation of herpes virus from the lesion has to be interpreted with caution in the absence of supporting serological evidence. The two other children who had clinical recurrences of febrile stomatitis were not investigated. There is thus insufficient evidence to refute the statement that the acute stomatitis never returns (Court 1963), although it is more in line with Craig's opinion (1945) that herpetic stomatitis is apt to recur. Anderson and Hamilton (1949) recorded two instances in twenty patients followed for one year. Scott et al. (1941) clearly recognize that recurrent stomatitis may occur at any age after primary infection in the same way as recurrent herpes of the lips and elsewhere. Burnet (1946) sums up the situation thus: "After recovery the child is/

Fig. 27



N.F. ♀ 2 years
+

Date of primary infection uncertain

Recurrent facial lesion

Herpes simplex virus isolated

Complement fixation titres 1/128 → 1/128

is probably immune from any manifestation of herpes as severe as the initial one, but it is obvious that no absolute immunity is induced". Such a view might explain the recurrences of oral ulceration without systemic upset observed (mainly by their parents) in thirteen other children in the present studies. Clinically, such lesions as I saw, closely resembled aphthae. A possible - and attractive - explanation is that the children had gone on to develop simple aphthae, as a result of the herpetic infection. The literature is full of deterrents to such facile "post hoc ergo propter hoc" reasoning.

APHTHAE AND HERPETIC STOMATITIS.

Concerning aphthous ulceration, Bodley Scott(1965) states "All efforts to incriminate a virus have failed, and in particular herpes virus is not responsible". Sircus et al. (1957) came to the same conclusion. In the present studies, the control child for case No.39, a girl of ten years, suffered from simple recurrent aphthae (as did her two sibs): antibodies to herpes virus were not found in her serum. The relationship between herpetic stomatitis and aphthous ulceration, if it should exist, is not a direct one. Recent work by Lehner (1964) might be relevant in this context. Using tanned sheep red cells coated with an extract of oral mucosa, he showed that sera from patients with aphthous ulcers caused a specific agglutination in higher titre and greater proportion than did those of controls and of other diseases. He feels the evidence suggests more than an immunological reaction to non-specific mucosal damage, and he postulates an antibody cross-reacting with an infecting/

infecting agent and oral mucosa. Such a hypothesis might explain some of the instances of recurrent oral ulceration without systemic upset exhibited by children in the present studies, but the co-incident and unrelated development of simple aphthous ulceration cannot be excluded.

The finding of three cases of erythema multiforme in the group of children who had suffered from herpetic stomatitis might be dismissed as purely fortuitous. On the other hand, there are several reports associating the skin disorder with recurrent herpes simplex (Anderson 1945, Rook 1947, Anderson et al. 1949, Pandi 1964). At best, the association is not a simple one of cause and effect, but there is little doubt that an attack of herpes simplex may trigger off erythema multiforme (Holti 1967). The interval between the primary stomatitis and the onset in the three cases in this series is so long that an aetiological relationship seems tenuous. The situation is summed up by Brain (1951) as follows:

"While it is not difficult to recover the virus of herpes from the herpetic lesions and sometimes the buccal and nasal mucosa of such cases (i.e. erythema multiforme showing associated recurrent herpetic lesions), reports of the isolation of herpes virus from the lesions of erythema multiforme are so rare that this virus cannot be incriminated as an aetiological factor".

MANAGEMENT / (1965) report the use of anti-herpes vaccine (in an established case).

MANAGEMENT

Discussion, which has centred mainly on the problems of clinical diagnosis, would be incomplete without reference to therapy. Despite recent advances in antiviral agents, such as idoxuridine, a safe effective specific remedy is not yet available. Therapeutics thus becomes more a matter of "management" than of definitive "treatment". Parental anxiety has been mentioned as an important feature, and this the family doctor must attempt to allay: for parents need a quiet optimistic expectancy to help them cope with disturbed nights and a miserable child. This confidence will be sadly undermined when the doctor's reassuring "It's only teething" is superceded by "Trench mouth - a dirty mouth, mother", or when "It's only a cold" becomes a seriously debilitating ulcerative stomatitis. The importance of making an early correct and firm diagnosis, and adhering to it, is thus obvious. The child's refusal to take anything by mouth may lead to severe dehydration and ketosis; it is reasonable to advise the pushing of fluids, and to reassure the parents that the child will eat when he is ready. The absence of a specific remedy has not deterred physicians from advocating a long list of medicaments. Lichenstein et al. (1964) mention the following: antibiotics, antihistamines, cortcoids, lysozyme, pantothenic acid, poliomyelitis vaccine, trypsin and vitamins, to which they add lactobacillus acidophilus. Carter (1962) lists anaesthetic lozenges, maple syrup, protamide, smallpox vaccination and γ -globulin. Bolgert and Tinthoin (1965) report the use of anti-herpes vaccine (in an established case).

CONCLUSION Scott et al. (1941) sum up the situation in the words "The disease, then, appears to be self-limited, and conclusions as to the benefits of various therapeutic agents must be based on this knowledge".

The children in this series occasionally received oral antibiotics exhibited on the basis of wrong initial diagnosis: ultimately most received only paediatric aspirin mixture N.F., which, in the small doses administered, caused none of the disasters mentioned by Craig et al. (1966).

PREVENTION

There is need to develop active measures to prevent the disease. Antibody studies in the present work confirm the fact that the virus is extremely widespread in the community. It is therefore unrealistic to try to shield children completely from exposure to the virus. Scott et al. (1941) state that even although a mother may not show clinical evidence of herpetic labialis she may still possibly provide a focus of infection for her susceptible child. Nevertheless, a first step might be to promote awareness of the potentially infectious nature of the common cold sore as an exercise in Public Health education. There is a case to be made out for the development of a vaccine, as Anderson and Hamilton (1949) suggest, although such a measure has not met with success so far.

CONCLUSION /

CONCLUSION

The evidence concerning the nature of a form of febrile stomatitis affecting fifty children is discussed in the light of recent relevant published work. It is concluded that this condition is primary herpetic stomatitis. It is seen more frequently in general practice than in hospital. Attention is drawn to the early presenting features, chief of which is respiratory catarrh. Because the presenting symptoms, apart from the oral ulceration, are common to the early phases of many other conditions in general practice, the disease is not as clear-cut as consideration of the clinical features in isolation would suggest. Even the obvious oral ulceration tends to be explained away in terms of "Vincent's infection" or "thrush", for reasons which are briefly discussed.

The differential diagnosis, which is potentially fairly wide, is limited in practice to a few conditions, mainly of virus origin. The implications of incorrect diagnosis are examined in the light of the potentially pathogenic role of herpes simplex virus at any given time, and when cases of infection are studied "in depth".

The probable and possible sequelae are discussed, and it appears that about half the children with herpetic stomatitis have developed recurrent skin lesions within a short time. This liability tends to persist.

The controversial issue of a possible relationship between herpetic stomatitis and recurrent oral ulceration is discussed in the light of the findings of this study and of published reports. There may be more than one explanation, and the possibility of an auto-immune mechanism is entertained.

The incidental finding of erythema multiforme in a small number of former sufferers from herpetic stomatitis is not considered to be significant in view of the lack of supporting evidence of a close aetiological relationship shown in the literature

The importance of an early correct and firm diagnosis to the management of the anxious family is stressed in the discussion of treatment and prophylaxis. This can be achieved by keeping in mind the possibility of herpetic stomatitis each time a child aged one or two years presents with febrile upper respiratory catarrh.

PRIMARY HERPETIC GINGIVO-STOMATITIS

Clinical Studies from General Practitioner

Primary herpetic gingivo-stomatitis, a well-defined clinical entity, appears to present a peculiarly difficult diagnostic challenge to the family doctor. Possible reasons for this have been examined in a series of studies over a period of three years by one general practitioner in a large group practice.

SUMMARY of THESIS

presented for the degree of
 Analysis of the early clinical manifestations of the disease, studied in DOCTOR of MEDICINE, showed upper respiratory catarrh to be a prominent feature. The difficulty of spotting this and other early features of the disease by
 James D.E. Knox, M.B., Ch.B., M.R.C.P.Ed.
 against the more common illnesses was demonstrated in a one-year prospective survey of all febrile children seen by this family doctor.

PRIMARY HERPETIC GINGIVO - STOMATITIS
 Laboratory studies led to
 antibody studies in a control group,
 and of mothers of both groups. The findings supported the clinical diagnosis, confirmed the high prevalence of infection in the mothers, and provided information on some changes in antibody response in relation to the length of the follow-up period.

Recurrent/

Primary herpetic gingivo-stomatitis, a well-defined clinical entity, appears to present a peculiarly difficult diagnostic challenge to the family doctor. Possible reasons for this have been examined in a series of studies over a period of three years by one general practitioner in a large group practice.

Analysis of the early clinical manifestations of the disease, studied in a prospective survey, showed upper respiratory catarrh to be a prominent feature. The difficulty of spotting this and other early features of the disease against the background of similar presentations of different - and more common - illnesses was demonstrated in a one-year prospective survey of all febrile children seen by this family doctor.

Laboratory support for the main clinical survey led to antibody studies of affected children, of a control group, and of mothers of both groups. The findings supported the clinical diagnosis, confirmed the high prevalence of infection in the mothers, and provided information on some changes in antibody response in relation to the length of the follow-up period.

Recurrent/

Recurrent clinical infections and possible sequelae were already evident, even within the relatively short duration of the survey. These phenomena, examined against the control group employed in the antibody studies, included herpes facialis, various infections, and recurrent mouth ulceration.

The findings were compared with results of a retrospective study of cases of probable herpetic stomatitis and of control children, selected from the group practice records. Similar results were obtained in this survey.

Comparison of households containing affected children against others from the practice showed the disease occurred more frequently in a setting of poor hygiene and larger sized families, factors which also hinder the family doctor in diagnosis.

From the pattern of admission diagnoses of cases treated in the Edinburgh City Hospital during the three years of the studies, it was clear that other general practitioners in the area shared difficulties in diagnosis.

The results of all these surveys have been examined in the light of published reports, with particular reference to diagnosis in general practice. The differential diagnosis has/

has been discussed and illustrated by examples drawn from the day-to-day work of the practice.

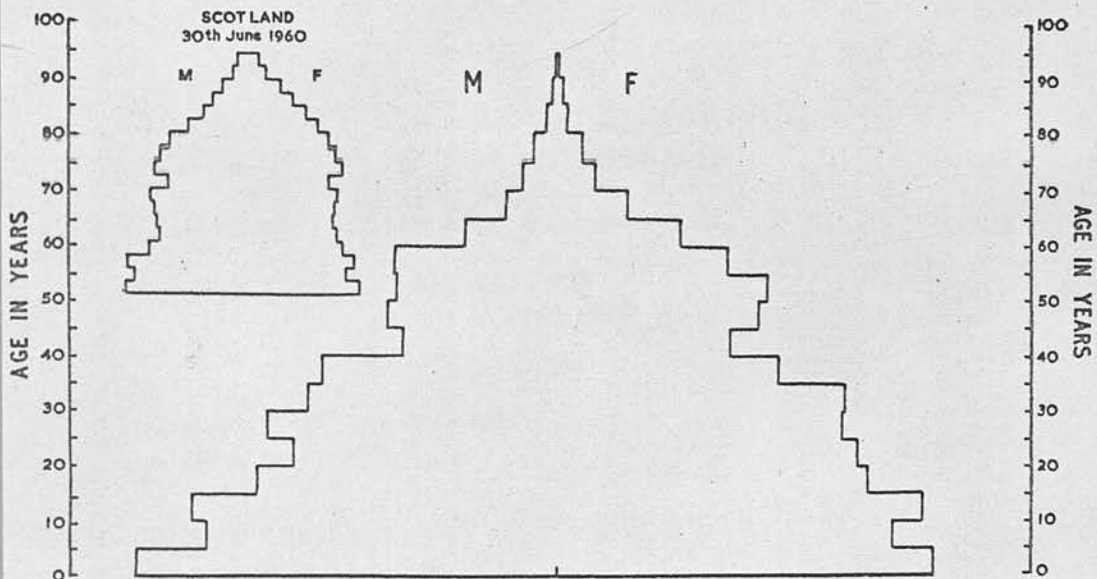
It is concluded that greater attention should be paid to the disease - which is as common as rubella, mumps or the more severe cases of chickenpox - in undergraduate teaching and in post-graduate research.

The inadequacy of drug therapy highlights the importance of prophylaxis, and a greater public awareness of the potentially infectious nature of the common "cold sore" needs to be promoted.

APPENDIX 1

APPENDIX 2

EDINBURGH PRACTICE POPULATION — PERCENTAGE AGE AND SEX DISTRIBUTION
October 1st 1960



A LARGE TEMPORARY HOUSING AREA OF PREFABS WAS PULLED
DOWN TO MAKE ROOM FOR PERMANENT BUILDINGS

APPENDIX 2

DYNAMICS OF THE PRACTICE POPULATION











PATIENTS ON LIST AT 31st DECEMBER 1962	20,014
PATIENTS ON LIST AT 31st DECEMBER 1965	20,863
PATIENTS LEAVING LIST IN 1964	1,279
PATIENTS LEAVING LIST IN 1965	1,413*
PRINCIPALS IN PARTNERSHIP	7

* A LARGE TEMPORARY HOUSING AREA OF PREFABS WAS PULLED
DOWN TO MAKE ROOM FOR PERMANENT BUILDINGS

APPENDIX 3

PRIMARY H. SIMPLEX
SEASONAL INCIDENCE
50 Cases

 = NOT RECORDING

	JAN.	FEB.	MAR.	APR.	MAY	JN.	JY.	AUG.	SEP.	OCT.	NOV.	DEC.	ANNUAL TOTALS	
1963												0	1	1
1964	0	0	1	2	1	2	 2	1	2	1			12	
1965	3	0	3	0	3	2		1	2	3	2	1	20	
1966	1	0	3	4	3	3		3					17	
TOTALS	4	0	7	6	7	7	2	5	4	4	2	2		

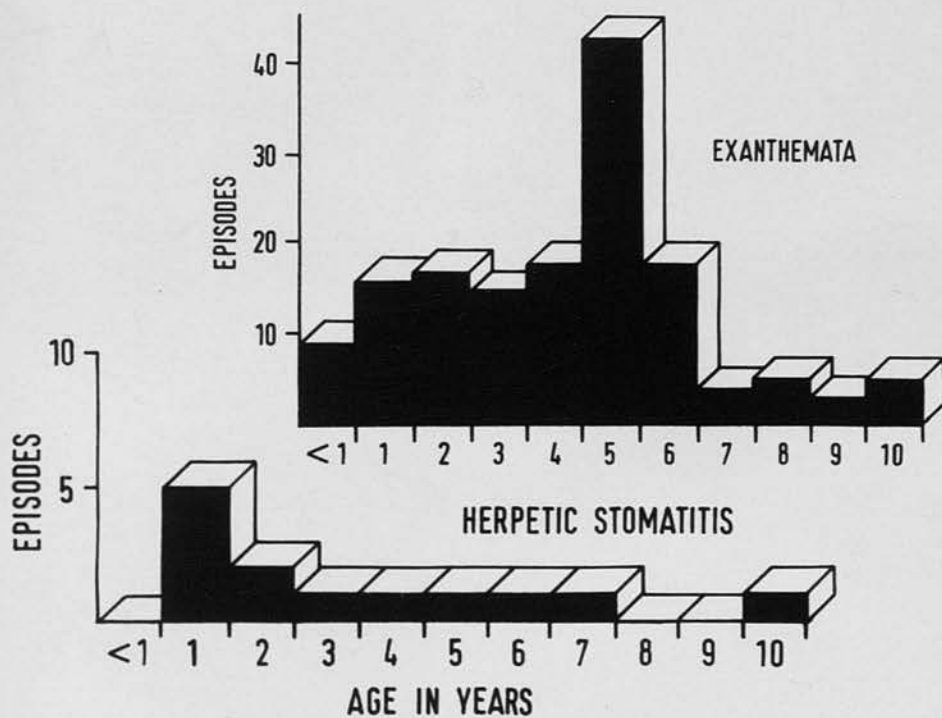
MAP OF PART OF PRACTICE AREA

- Case of stomatitis during survey
- Families with young children normally attended



APPENDIX 5

FEBRILE ILLNESSES IN CHILDREN.
EXANTHEMATA AND HERPETIC STOMATITIS : 1 YEARS EXPERIENCE.
EPISODES BY AGE.



APPENDIX 6

**PRIMARY H. SIMPLEX. 50 Cases.
DISTRIBUTION BY AGE AND SEX.**

AGE	MALE	FEMALE	TOTAL
< 1	1	0	1
1	11	10	21
2	6	4	10
3	0	4	4
4	1	1	2
5	3	0	3
6	1	1	2
7	1	2	3
8	1	0	1
9	0	1	1
10	1	1	2
TOTALS	26	24	50

APPENDIX 7

MATCHING OF FORTY-ONE PAIRS OF HOUSEHOLDS

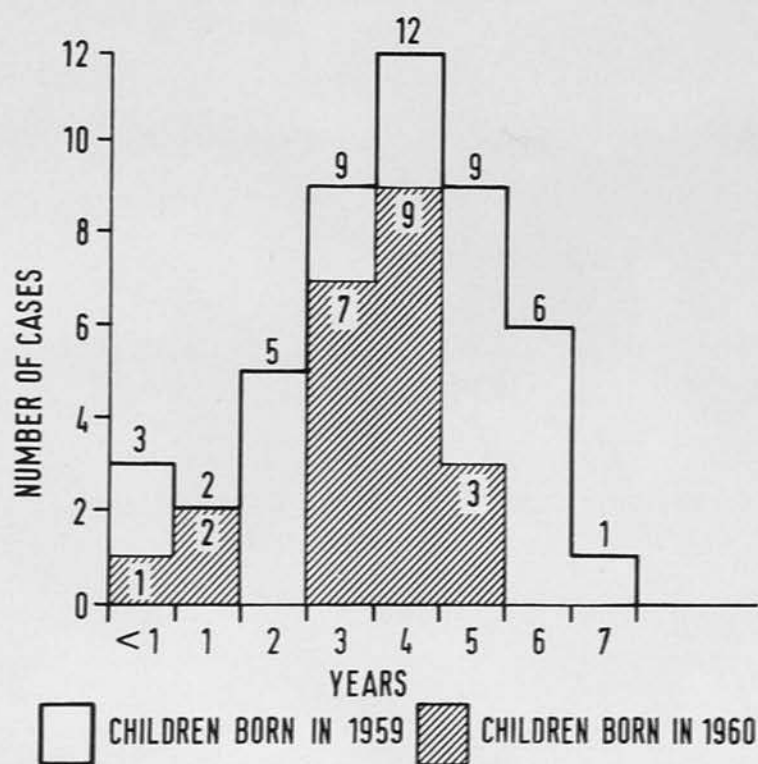
Parameters not used in selection

DISTRIBUTION OF 47 CHILDREN BY
DURATION OF FOLLOW-UP

	<u>INDEX</u>	<u>CONTROL</u>
a) Sex of children under 12 years:		
Number of males	79	77
Number of females	66	65
b) Differences between matched pairs in respect of children under 12 years:		
Number of households with:		
1 additional child	4	4
2 additional children	0	0
3 additional children	1	0
c) Households where father is not registered with the practice	7	8

APPENDIX 8

DISTRIBUTION OF 47 CHILDREN BY
DURATION OF FOLLOW-UP



APPENDIX 9

HOUSING



a) Traditional Housing built 1948



b) Modern flats built early 1960s

APPENDIX 10
 SUMMARY OF FOURTEEN CASES ADMITTED TO EDINBURGH CITY HOSPITAL
 DURING THE SURVEY 1963 - 1966

Case Number	Sex	Age	Admission Diagnosis	Comment
1	M	1	? Meningitis	
2	M	10/12	? Vincent's angina	Splenomegaly and adenopathy, atypical mononuclears. Paul Bunnell -ve
3	F	2	"Diarrhoea" and tonsillitis	C.F. antibody titre 8 → 256 (Reciprocal)
4	F	1	Impetigo of face	Pustular lesion R middle finger
5	M	2	Tonsillitis	
6	M	1	Tonsillitis	
7	F	2	? Measles	T 104 ⁸ Sister of case No.6.
8	F	6	? Vincent's angina	
9	F	1	P.U.O.	Transient scarletiform rash prior to admission
10	M	1	Gastro-enteritis	
11	F	2	Herpetic stomatitis	Case No.26 G.P. series
12	M	2	"Stomatitis"	
13	M	10	? Glandular fever	
14	F	1	Acute gingivitis	Splenomegaly: conjunctivitis

APPENDIX 11

PRIMARY HERPETIC STOMATITIS

DIFFERENTIAL DIAGNOSIS

Diagnosis on admission to hospital of forty-three children, Glasgow.

(Duncan and Ross 1966)

<u>Admission Diagnosis</u>	<u>Number of Patients</u>
"Thrush or trench mouth"	20
"Cerebro-spinal meningitis"	10
"Glandular fever"	3
"P.U.O."	3
Herpetic stomatitis	3
"Tonsillitis"	2
"Pneumonia"	2
Total	<u>43</u>

APPENDIX 12

SUMMARY OF SOME FEATURES OF THE FIFTY CASES OF HERPETIC STOMATITIS

Case Number	Sex	Age	Digital Lesion	Virus Isolated	Follow-up Months	Subsequent Mouth Lesions	Presentations
1	A.M.	F	7	-	34	+	+
2	S.M.	M	2	-	31	-	+
3	A.F.	F	4	-	31	-	+
4	S.B.	M	2	-	30	+	+
5	S.A.	F	1	-	25	-	+
6	O.F.	F	1	-	23	-	+
7	S.S.	F	10	-	27	-	+
8	S.D.	F	1	-	27	-	+
9	S.E.	M	4	-	27	-	+
10	J.M.	M	9	-	37	-	+
11	S.F.	M	1	-	25	-	+
12	S.S.	F	3	-	25	-	+
13	A.D.	M	1	-	Moved from district	-	+
14	S.G.	F	2	-	22	-	+
15	C.S.	F	1	-	Moved from district	-	+
16	S.W.	M	1	-	Moved from district	-	+

APPENDIX 12

SUMMARY OF SOME FEATURES OF THE FIFTY CASES OF HERPETIC STOMATITIS
SEEN IN GENERAL PRACTICE 1963-66

Case Number	Sex	Age	Digital Lesion	Virus Isolated	Follow-up Months	C.F. Titre Reciprocals	N.T. Reciprocals	Comment	Subsequent Herpes:Ulcer	Mouth	Presentation Difficult
1	A.M.	F	7	-	/	32	256	Sister of case No.2			
2	S.M.	M	2	-	/	64	/		+		+
3	A.F.	F	4	-	/	64	≥256	Sister of case No.11	+		+
4	S.B.	M	2	+	-	32	≥256	Conjunctivitis	+		
5	S.A.	F	1	-	/	64	256		+		
6	C.F.	F	1	-	/	8	≥256		+		
7	C.M.	F	10	-	/	32	256				
8	D.D.	F	1	-	/	32	≥256				
9	J.R.	M	6	-	/	16	256	Brother of case No.49	+		
10	J.M.	M	5	-	/	32	256	Severe abdominal pain	+		
11	S.F.	F	1	-	/	32	/		+		+
12	K.H.	F	3	-	/	8	≥256				+
13	A.D.	M	1	-	/	Moved from district					
14	S.G.	F	2	-	/	8	32	E.Multiforme 16/12 later			+
15	C.S.	F	1	-	/	Moved from district					
16	J.W.	M	1	-	/	Moved from district					+

APPENDIX 12 contd.

Case Number	Sex	Age	Digital Lesion	Virus Isolated	Follow-up Months	C.F. Titre	N.T. Reciprocals	Comment	Subsequent	
									Herpes:Ulcer	Mouth Presentation Difficult
17	D.W.	F	1	-	19	16	128			
18	Y.B.	F	1	-	19	8	128			
19	H.C.	F	3	-	19	8	256			+
20	D.H.	M	1	+	17	32	/			
21	R.H.	M	1	-	17	8	≥ 256			+
22	E.M.	F	1	-	16	16	128			+
23	J.W.	M	1	-	16	32	/		+	
24	L.B.	F	4	-	16	16	≥ 256			
25	B.M.	F	1	-	14	< 8	128	Transient urticaria		
26	M.S.	F	2	-	12	256	256	Admitted hospital		
27	P.M.	M	1	+	12	No specimen				
28	V.O.	F	2	-	12	64	128			
29	A.M.	M	5	-	12	+	128	Also faucial ulcers		
30	H.D.	M	8	-	12	32	32	? Herpes simplex U.R.I. later		+
31	E.D.	F	2	-	11	16	128			+
32	A.N.	M	2	-	10	64	/			
33	G.P.	F	2	-	10	128	/			+
34	M.D.	M	1	+	8	64	128			+

* Serum anti-complementary

APPENDIX 12 contd.

Case Number	Sex	Age	Digital Lesion	Virus Isolated	Follow-up Months	C.F. Titre Reciprocals	N.T. Reciprocals	Comment	Subsequent Herpes:Ulcer	Mouth	Presentation Difficult	
35	H.P.	M	1	-	+	7	16	32		+		
36	M.H.	M	1	+	/	6	64	/	Source of infection, Case No.39	+		
37	K.C.	M	10/12	-	/	6	64	/		+		
38	H.W.	F	7	-	/	6	256	/	Sister of case No.40	+		+
39	M.B.	F	9	-	+	6	256	≥ 256	Marked systemic upset, rising titre C.F. antibody	+		+
40	C.W.	F	1	-	+	6	32	/		+		
41	J.M.	F	2	-	+	5	16	128				
42	K.S.	M	5	-	+	5	64	/	Brother of case No.43			
43	D.S.	M	2	-	+	5	32	128				
44	D.R.	M	10	-	+	4	64	128	Brother of case No.45			
45	M.R.	M	7	+	+	4	64	64		+		+
46	D.M.	M	1	-	+	4	32	/	Morbilliform rash			
47	M.S.	F	3	-	+	3	8	8	Rubelliform rash			+
48	F.D.	M	6	+	+	2	32	128	Virus form throat swab	+		+
49	G.R.	M	1	-	/	2	< 8	/	Diarrhoea			+
50	R.M.	M	2	-	/	1	32	/				

APPENDIX 13

APPENDIX 13 contd.

ANTIBODY STUDIESRECIPROCAL OF TITRES

Case Number	INDEX		CONTROL		INDEX MOTHER			CONTROL MOTHER		
	CF	NT	CF	NT	CF	NT	Herpes Labialis	CF	NT	Herpes Labialis
1	32	256	32	256	64	256	+	32	≥ 256	-
2	64	/	16	128	See Case No. 1.					
3	64	≥ 256	64	≥ 256	32	≥ 256	+	32	≥ 256	+
4	32	≥ 256	64	≥ 256	32	128	-	16	≥ 256	-
5	64	256	32	≥ 256	64	≥ 256	-	16	≥ 256	-
6	8	≥ 256	32	128	16	≥ 256	-	128	≥ 256	-
7	32	256	< 8	< 8	32	256	+	64	≥ 256	+
8	32	≥ 256	< 8	< 8	32	16	-	64	8	-
9	16	256	< 8	< 8	16	≥ 256	-	64	≥ 256	-
10	32	256	< 8	< 8	64	≥ 256	-	16	256	-
11	32	/	< 8	< 8	See Case No. 3.					
12	8	≥ 256	< 8	< 8	64	≥ 256	-	16	≥ 256	-
13	Moved from District									
14	8	32	< 8	< 8	16	≥ 256	+	64	≥ 256	-
15	Moved from District									
16	Moved from District									
17	16	128	< 8	< 8	32	≥ 256	-	32	≥ 256	+
18	8	128	< 8	< 8	16	256	+	32	≥ 256	+
19	8	256	< 8	< 8	8	128	-	< 8	16	-
20	32	/	< 8	< 8	16	≥ 256	+	16	128	+
21	8	≥ 256	< 8	< 8	8	8	-	64	≥ 256	-
22	16	128	< 8	< 8	32	128	-	64	≥ 256	+
23	32	/	16	≥ 256	16	128	-	16	64	-
24	16	256	< 8	< 8	32	256	-	64	≥ 256	-
25	< 8	< 8	16	128	32	64	+	16	≥ 256	+
26	256	256	128	/	32	256	+	64	/	+
27	No. spec.		No Spec.		64	128	+	No Spec.		-
28	64	128	< 8	< 8	64	≥ 256	-	16	≥ 256	+
29	+	128	32	≥ 256	8	128	-	32	≥ 256	-

30 /

* Serum anti-complementary

APPENDIX 13 contd.

Case Number	INDEX		CONTROL		INDEX MOTHER			CONTROL MOTHER		
	CF	NT	CF	NT	CF	NT	Herpes Labialis	CF	NT	Herpes Labialis
30	32	32	No spec.		32	64	-	32	64	-
31	16	128	< 8	< 8	16	≥256	-	32	≥256	+
32	64	/	< 8	< 8	32	≥256	-	16	≥256	-
33	128	/	< 8	/	32	128	+	32	128	+
34	64	128	< 8	< 8	64	≥256	+	32	256	-
35	16	32	< 8	/	16	256	+	< 8	< 8	-
36	64	/	< 8	< 8	32	128	+	< 8	< 8	-
37	64	/	< 8	/	8	256	+	32	128	-
38	256	/	< 8	< 8	16	128	-	64	≥256	-
39	256	≥256	< 8	< 8	64	≥256	+	64	≥256	-
40	32	/	< 8	/	See Case No. 38					
41	16	128	64	/	32	≥256	+	64	≥256	+
42	64	/	< 8	< 8	32	≥256	+	16	≥256	-
43	32	128	< 8	< 8	See Case No. 42					
44	64	128	< 8	< 8	< 8	< 8	-	32	≥256	-
45	64	64	< 8	< 8	See Case No. 44					
46	32	/	256	/	64	128	+	32	≥256	+
47	8	8	< 8	< 8	16	256	-	32	128	+
48	32	128	8	8	64	≥256	-	32	≥256	-
49	< 8	/	< 8	< 8	See Case No. 9					
50	32	/	< 8	/	16	256	+	64	≥256	-

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