nant disease of the breast and 307 had benign disease. These women with suspected malignancy were offered further investigation. If lesions were confirmed, the surgical opinion of a consultant was sought.

At the time of writing, 12 months after the end of the survey, biopsy had been carried out in 13 patients, in all of them proving benign. Eleven further patients in whom a repeat thermogram was again suspicious of malignancy were still under surveillance.

Discussion

The results of this survey indicate that the diagnostic accuracy of thermography and 70-mm. mammography does not approach that of clinical examination in patients with symptomatic breast disease. Thus, while one clinician correctly diagnosed malignant disease in 82% of women with breast complaints, the best possible accuracy, as represented by the highest individual accuracy when three radiologists independently surveyed the films, was only 53% for thermography and 61% for 70-mm. mammography. Even when one correct report from any of the three radiologists was considered, the accuracy was only 68% for thermography and 71% for 70-mm. mammography. Therefore neither thermography nor 70-mm mammography is suitable for use *as an isolated procedure* in the diagnosis of breast disease. Nor can either method of examination be used *in isolation* as a screening procedure. Indeed, we consider it dangerous to use each method alone, as it would give the patient false security.

Furthermore, there is considerable observer error between radiologists using these two methods: thus all three radiologists agreed with the diagnosis in less than one-third of cases. A single radiologist reporting either thermogram or 70-mm. mammogram films is likely to be inaccurate in a significant proportion of cases. The inaccuracy of 70-mm. mammography is partly explained by the technical difficulty of getting films of satisfactory quality though possibly with improved technique it may be of more value. The use of these methods as complements to clinical examination improved the diagnostic rate, but in all the patients in whom this occurred a palpable lump was present.

The incidence of false-positive reports as assessed in patients with benign disease and asymptomatic women is high. This has led to a considerable expenditure of time and money for the further investigation of suspect patients. As the number of asymptomatic women studied was relatively small and many were young, it is not surprising that no cancers have come to light in this group.

There is a current tendency to promote screening programmes for breast cancer with a single method of examination. Many such programmes have been set up and are generally uncontrolled. The reports of the New York group indicate that neither clinical examination nor mammography alone is an adequate method of screening, and our survey indicates clearly that thermography and 70-mm. mammography have no place as isolated screening procedures.

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Secretory IgA in Urinary Tract Infections

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Summary: Secretory IgA, measured by radial immunodiffusion, was compared in the urine of children with chronic and recurrent non-obstructive urinary tract infections with that in normal children. IgA, IgG, and IgM were also measured. Absent and low levels of IgA(s) were found in both groups; however, the mean levels of IgA(s) were significantly higher in the infected group compared with normals—3·3 to 0·78 mg./24 hours, respectively. Secretory IgA was found to be locally produced in the bladder. It is suggested that IgA(s) levels reflect an antibody response to infection.

Introduction

In some body secretions such as tears, saliva, and those of the gastrointestinal tract, secretory IgA (IgA(s)) is the predominant immunoglobulin (Chodirker and Tomasi, 1963; Tomasi and Zigelbaum, 1963). This IgA is chemically and immunologically distinct from serum IgA (Pollak *et al.*, 1968), and its role in the local immune defence system of the respiratory, and gastrointestinal tracts has been shown by finding in those secretions naturally occurring antibodies of the IgA class to viruses and bacteria and by the viral neutralizing activity of human nasal secretions after poliovirus and influenza infections (Rossen *et al.*, 1966; Bellanti *et al.*, 1967; Bellanti, 1968; Tourville *et al.*, 1968).

The recent finding of IgA(s) in normal human urine (Bienenstock and Tomasi, 1968) and the suggestion that urinary IgA may participate in local immune defence mechanisms led us to study the role of IgA(s) in non-obstructive chronic and recurrent urinary tract infections in children.

Patients and Methods

The study included 29 patients (10 normal children, 17 with urinary tract infection (one a newborn), and two with ileal bladders). All patients with urinary tract infections had either chronic or recurrent (three or more) infections without evidence of significant anatomical or functional abnormalities as defined by intravenous pyelogram, cystourethrogram, cystoscopy, and creatinine clearance.

Specimens.—Twenty-four-hour urine samples were

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collected from all children, and, whenever possible, during acute infections and remissions. Urines were preserved in 0·1% sodium azide, filtered on Whatman No. 1 paper, and concentrated 20 to 200 fold by Diaflo ultrafiltration (Pollak *et al.*, 1968). Total quantitative protein was measured with Tsychiyas reagent (Shevsky and Stafford, 1923), and urines were quantitated for IgA(s), IgA, IgG, and IgM by radial immunodiffusion using monospecific rabbit antisera to human IgA, IgG, and IgM (Uehling *et al.*, 1970).

Antisera.—Monospecific rabbit antihuman IgA(s) was prepared from human colostral secretory IgA by David T. Uehling, Mary Wilhemy, and E. R. Stiehm and kindly donated by them. The specific antisera measured either IgA(s) or free secretory "piece," or both, if present in the urine. Results were read in milligrams of intact colostral IgA(s) globulin per 100 ml. and expressed as mg./24 hours. The sensitivity of the method was 0·31 mg./100 ml. for IgA(s), 0·23 mg./100 ml. for IgA, 0·09 mg./100 ml. for IgG, and 0·50 mg/100 ml. for IgM.

Results

Total quantitative proteins were normal in all patients, ranging from 1·8 to 125 mg./24 hours, with a mean of 14·6 mg. IgM was noted in only one patient, who also had the highest levels of IgA(s), IgA, IgG, and total protein. IgG immunoplates were designed to measure low levels, and since a number of values were beyond the upper limits of the plates, no comment can be made regarding the correlations between IgG and other immunoglobulins.

IgA was present in all patients except one, a newborn with urinary tract infection. IgA(s) was also absent in this patient. IgA(s) levels tended to be higher than IgA in the patients with urinary tract infection. The reverse was observed in normals. IgA levels between the two groups, however, were not significantly different, with a mean of 1·2 mg./24 hours in normals and 1·4 mg./24 hours in infected individuals.

IgA(s) levels in normals ranged from 0 to 4·8 mg./24 hours, with a mean of 0·78 mg./24 hours (see Table). In the 17 patients with urinary tract infection, the range was 0-14·0 mg./24 hours, with a mean of 3·3 mg./24 hours. When calculated on a mg./ml. basis the means are respectively 0·0017 mg. and 0·0067 mg. If one excludes the newborn the latter value is then 0·0071 mg. The differences between means for both calculations are significant. No correlations were noted between IgA(s) levels and duration or severity of the patient's symptomats, the presence or absence of infection at the time of measurement, age, sex, or total protein excretion.

Urinary Immunoglobulin Levels. All values are in mg./24 hours

Case No.	Age in Years	Sex	Diagnosis	IgA(s)	IgA	IgG	IgM	Total Protein
1	7	M.	Normal	0	0·5	4·9	0	10·6
2	4	M.	Normal	0	0·4	6·0	0	8·2
3	12	M.	Normal	0	0·8	4·9	0	8·2
4	7	F.	Normal	0·8	0·5	5·8	0	4·1
5	4	F.	Normal	4·8	6·2	0	0	10·0
6	6	F.	Normal	2·2	1·2	0	0	53·5
7	10	F.	Normal	0	0·6	4·5	0	21·8
8	11	F.	Normal	0	0·8	4·5	0	2·2
9	1	F.	Normal	0	0·8	4·5	0	30·0
10	12	F.	Normal	0	0·2	1·1	0	3·7
11	6	F.	U.T.I.	14·0	0·6	5·8	0	8·4
12	13	F.	U.T.I.	0	2·2	0	0	15·4
13	6	F.	U.T.I.	7·0	0·4	3·2	0	1·8
14	8	F.	U.T.I.	6·8	0·4	6·0	0	10·3
15	9	F.	U.T.I.	4·0	0·4	6·0	0	2·0
16	NB	M.	U.T.I.	0	0	1·8	0	12·8
17	2	F.	U.T.I.	2·8	0·4	4·5	0	20·8
18	10	F.	U.T.I.	0	0·4	3·1	0	12·5
19	8	F.	U.T.I.	9·6	0·6	4·5	0	8·4
20	4	F.	U.T.I.	0	2·0	4·5	0	16·6
21	8	F.	U.T.I.	2·8	0·6	4·5	0	15·6
22	6	F.	U.T.I.	3·0	0·8	4·5	0	35·0
23	5	F.	U.T.I.	3·2	0·2	2·4	0	11·1
24	12	F.	U.T.I.	3·2	4·8	4·5	0	48·6
25	5	F.	U.T.I.	0	0·8	3·7	0	20·7
26	2	F.	U.T.I.	0	0·4	3·5	0	21·7
27	10	F.	U.T.I.	2·0	0·8	4·0	0	12·5
28	12	F.	Ileal bladder	0	0·6	0	0	31·2
29	4	F.	Ileal bladder	20·0	12·0	10·0	3·8	125·0
			Bladder wash	3·8	0·5	0·6	0	—

U.T.I. = Urinary tract infection.

Discussion

The normal serum ratios of immunoglobulins, being 85:10:5 for IgG, IgA, and IgM respectively, do not hold for body secretions (Chodirker and Tomasi, 1963; Tomasi and Zigelbaum, 1963), and the absence of any correlation between serum and non-vascular fluid levels of immunoglobulins has led to the postulate that secretory immunoglobulins provide a local defence mechanism (South *et al.*, 1968). This was supported by the finding that IgA(s) appears to be locally produced and secreted and that it is an 11S molecule which is chemically and immunologically distinct from serum IgA (Tomasi *et al.*, 1965; Bienenstock and Tomasi, 1968; Rossen *et al.*, 1968; Tourville *et al.*, 1968; Tomasi, 1969). The clinical importance of the IgA(s) system has been shown in the respiratory tract, where IgA antibodies appear after bacterial infection (Bellanti *et al.*, 1967) and where the lack of IgA(s) apparently predisposes to sinopulmonary infections (South *et al.*, 1968). Similar results have been obtained in the gastrointestinal tract (Crabbé and Heremans, 1966).

With the recent discovery of IgA(s) in the urine (Bienenstock and Tomasi, 1968) and the finding of IgA antibodies to *Escherichia coli* (Tourville *et al.*, 1968) it was suggested that the absence of IgA(s) in the urine might predispose to nonobstructive chronic and recurrent genitourinary infections of childhood. Secretory IgA is generally thought to be very low or absent in the newborn and therefore the absence of such in the one patient studied is not possible to interpret.

Our findings do not support this hypothesis. Though several patients had absent IgA(s), 7 out of 10 normals also had absent IgA(s). Indeed, IgA(s) levels tended to be much higher in patients with infection. The one normal who had high levels of IgA(s) might possibly represent previous asymptomatic and undiagnosed infection. The levels of IgA(s) in infected patients were also higher than those noted in normals by other authors (Bienenstock and Tomasi, 1968; Uehling *et al.*, 1970). Our findings correlate with those of Uehling and Stiehm (1969), who showed raised IgA(s) levels in a group of children with urinary tract infections, but these workers showed a significant correlation with age, since their younger patients tended to have lower levels of IgA(s). Our patients did not show such a correlation.

From our data IgA(s) levels probably indicate a local antibody response to infection, and its absence may not account for these infections. Though there are no exact levels of normal urine IgG, our work and that of others suggests that IgG antibodies occur as a local response to infection (Bienenstock and Tomasi, 1968; Tourville *et al.*, 1968). The IgA(s) levels noted in the urinary bladder of the patient with ureteral diversion supports the contention that IgA(s) is locally produced in the bladder. Its production in other areas of the genitourinary tract has been previously shown (Bienenstock and Tomasi, 1968).

Further studies are necessary to elucidate the local role of IgA(s) in the genitourinary tract. Since IgA does not fix complement it may act together with some other immunoglobulins or chemical factor to exert its effect on local defence mechanisms.

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Response of Asthmatics to Isoprenaline and Salbutamol Aerosols Administered by Intermittent Positive-pressure Ventilation

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Summary: The bronchodilator and cardiac effects produced by aerosols of 0·5% isoprenaline and of 0·25, 0·5, and 1% salbutamol administered in 40% oxygen by intermittent positive-pressure ventilation were compared in 24 asthmatic patients. Isoprenaline and salbutamol in concentrations of 0·5% were equipotent in peak bronchodilator effect; salbutamol was superior in total bronchodilator effect and duration of average effect, but the peak bronchodilator effect occurred earlier after isoprenaline. Significantly greater tachycardia was produced by 0·5% isoprenaline than by the same concentration of salbutamol. The 0·25, 0·5, and 1% concentrations of salbutamol had about the same peak bronchodilator effect, but there was a stepwise increase in total effect and duration of average effect in relation to the concentration used. A similar stepwise increase in heart rate was also noted, but with all concentrations this was significantly less than with 0·5% isoprenaline. It was concluded that a 0·5% solution of salbutamol, which provided maximal bronchodilatation without important tachycardia, was therapeutically superior to the other three treatments.

Introduction

The β-adrenergic stimulant isoprenaline administered by inhalation as an aerosol has until recently been used more often than any other sympathomimetic amine in the treatment of bronchial asthma. It has the disadvantage of producing undesirable cardiovascular side effects, and this has prompted search for an equally effective bronchodilator drug with a less pronounced action on the myocardium. Orciprenaline has proved disappointing in this respect because it is only slightly less prone than isoprenaline to increase the heart rate and blood pressure (Kennedy and Simpson, 1969). Another isoprenaline derivative, salbutamol, the pharmacological properties of which were first described by Hartley *et al.* (1968), is as effective a bronchodilator as isoprenaline and has a longer duration of action. It does not produce cardiovascular side effects when inhaled in the recommended dose (Choo-Kang *et al.*, 1969; Kennedy and Simpson, 1969), but when administered in larger doses by inhalation (Riding *et al.*, 1969), orally (Kennedy and Simpson, 1969), or intravenously (Warrell *et al.*, 1970) it has been shown to produce a slight increase in heart rate. Nevertheless, it is now being prescribed on a large scale in the treatment of bronchial asthma.

Because patients with access to bronchodilator aerosols are apt to exceed the recommended dosage, even when sternly warned not to do so, clearly it is important to determine whether salbutamol is less dangerous than isoprenaline when administered in large doses, particularly in conditions of hypoxia, such as exist in patients with status asthmaticus, in whom serious toxic effects are probably more likely to occur. When planning a study of this type it is important in the first instance, for reasons of safety, not to expose patients simultaneously to the possible dangers of high dosage and hypoxia. An evaluation of relative toxicity must also take into consideration the degree of benefit derived from the treatment given. This paper reports the first stage of such an investigation, in which we have compared in asthmatic patients *without significant hypoxia* the degree of bronchodilatation and tachycardia produced by salbutamol and isoprenaline administered by inhalation in the form of an aerosol. In the second stage, which will be reported in a later communication, hypoxic patients with status asthmaticus are being given a salbutamol aerosol by inhalation in a dose which has been shown in the first stage to produce the most favourable balance between bronchodilation and tachycardia.

One of the main problems in a study of this type, as Warrell *et al.* (1970) have pointed out, is to devise a reproducible technique for the inhalation of bronchodilator aerosols which will ensure that when a comparison is made between two drugs or between various doses of the same drug any difference observed is specifically related to these two variables. When pressurized dispensers are used it is unlikely that the whole of the prescribed dose ever reaches the bronchi. This in itself is not important, but, because there is a "hit or miss" element in the use of pressurized dispensers, the proportion of each dose reaching the bronchi must vary widely, and this will tend to blur differences between the effects of one drug and another, and between the effects of various doses of the same drug. In an attempt to resolve this problem it was decided in this study to administer nebulized diluted solutions of the drugs by intermittent positive-pressure ventilation (IPPV) for a period of three minutes, using a Bennett ventilator to deliver the aerosol to the patient through a tightly fitting facemask. With this technique it is of course not possible to measure the volume of solution which lodges in the bronchi, as some of the inhaled aerosol is sub-

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