

the milk concentration or the volume of milk consumed. A recent study carried out by Prentice (unpublished) in The Gambia has demonstrated that infants born to older mothers of high parity are likely to be at a considerable disadvantage, in terms of the mother's ability to produce milk rich in protective factors, compared with those born to young primiparous mothers. This finding and the effect of the stage of lactation indicate that there is a considerable spread of potential effectiveness within the breast-feeding community. The influence of maternal nutritional status also needs to be taken into account. Like nutritional investigations, studies on breast-milk immunology carried out within a public health framework could be very valuable in the development of practical health-improvement strategies.

THE FUTURE

Suggesting that much more research needs to be done is the expected reaction of a scientist. I am afraid, however, that a too emotional and scientifically unsubstantiated emphasis could begin to have a negative effect on the popularity of breast-feeding. Breast-feeding is important, and we must be able to define with greater confidence both its strengths and its limitations.

REFERENCES

- Ogra PL, Greene HL. Human milk and breast feeding: an update on the state of the art. *Pediatr Res* 1982; **16**: 266-71.
- Whitehead RG, Paul AA. Infant growth and human milk requirements: a fresh approach. *Lancet* 1981; **ii**: 161-63.
- James WPT, Trayhurn P. Thermogenesis and obesity. *Br Med Bull* 1981; **37**: 43-48.
- Rowland MGM, Paul AA, Whitehead RG. Lactation and infant nutrition. *Br Med Bull* 1981; **37**: 77-82.
- Prentice A, Prentice AM, Whitehead RG. Breast-milk fat concentrations of rural African women. 1. Short-term variations within individuals. *Br J Nutr* 1981; **45**: 483-94.
- Prentice A, Prentice AM, Whitehead BG. Breast-milk fat concentrations of rural African women. 2. Long-term variations within a community. *Br J Nutr* 1981; **45**: 495-503.
- Prentice AM. Variations in maternal dietary intake, birthweight and breast-milk output in The Gambia. In: Aebi H, Whitehead RG, eds. Maternal nutrition during pregnancy and lactation. Berne: Hans Huber, 1980: 167-83.
- Jelliffe DB, Jelliffe EFP. The volume and composition of human milk in poorly nourished communities: a review. *Am J Clin Nutr* 1978; **31**: 492-515.
- Rajalakshmi R. Gestation and lactation performance in relation to the plane of maternal nutrition. In: Aebi H, Whitehead RG, eds. Maternal nutrition during pregnancy and lactation. Berne: Hans Huber, 1980: 184-202.
- Bates CJ, Prentice AM, Watkinson M, et al. Riboflavin requirements of lactating Gambian women: a controlled supplementation trial. *Am J Clin Nutr* 1982; **35**: 701-09.
- Bates CJ, Prentice AM, Prentice A, Paul AA, Whitehead RG. Seasonal variations in ascorbic acid status and breast milk ascorbic acid levels in rural Gambian women in relation to dietary intake. *Trans Roy Soc Trop Med Hyg* 1982; **76**: 341-47.
- Rutishauser IHE, Burgess AP, Jones PRM, Krueger RH, Stanfield JP. Growth and development. In: Shaper AG, Kibuka Musoke JW, Hutt MSR, eds. Medicine in a tropical environment. London: British Medical Association, 1972: 227-37.
- Whitehead RG. Infant feeding practices and the development of malnutrition in rural Gambia. *UN Univ Food Nutr Bull* 1979; **1**: 36-41.
- McMillan JA, Landaw S, Oski FA. Iron sufficiency in breast fed infants and the availability of iron from human milk. *Pediatrics* 1976; **58**: 686-90.
- Fomon SJ. Infant nutrition. 2nd ed. Philadelphia: WB Saunders, 1974.
- Waterlow JC, Thomson AM. Observations on the adequacy of breast-feeding. *Lancet* 1979; **ii**: 238-42.
- McClelland DBL, McGrath J, Samson RR. Antimicrobial factors in human milk. *Acta Paediatr Scand* 1978; Supplement 271: 1-20.
- WHO/FAO. Energy and protein requirements. *WHO Techn Rep Ser* 1973; 522. *FAO Nutr Meetings Rep Ser* 1973; 52.
- Department of Health and Social Security. Recommended daily amounts of food energy and nutrients for groups of people in the United Kingdom. Report on Health and Social Subjects 1979; No. 15. London, HM Stationery Office, 1979.
- Whitehead RG, Paul AA, Cole TJ. A critical analysis of measured food energy intakes during infancy and early childhood in comparison with current international recommendations. *J Hum Nutr* 1981; **35**: 339-48.
- Whitehead RG, Paul AA, Cole TJ. Trends in food energy intakes throughout childhood from one to 18 years. *Hum Nutr Appl Nutr* 1982; **36**: 57-62.
- McKillop FM, Durnin JVG. A comparison of the energy and nutritional intakes of 305 Glasgow infants with current recommendations for the UK. *Proc Nutr Soc* (in press).
- Editorial. The how of breast milk and infection. *Lancet* 1981; **i**: 1192-93.
- Blanc B. Biochemical aspects of human milk—comparison with bovine milk. *World Rev Nutr Diet* 1981; **36**: 1-19.
- Goldman AS, Garza C, Nichols BL, Goldblum RM. Immunologic factors in human milk during the first year of lactation. *J Pediatr* 1982; **4**: 563-67.

Hospital Practice

HOW NECESSARY ARE SPECIFIC IgE ANTIBODY TESTS IN ALLERGY DIAGNOSIS?

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Summary In a 12-month study 301 patients referred to hospital consultants with putative allergic symptoms were tested for specific IgE antibodies to a panel of allergens and for total serum IgE levels. Examination of the data in relation to clinical information and the results of skin prick tests showed that the specific IgE antibody test has a limited role in the investigation of such patients.

INTRODUCTION

THERE is abundant evidence that acute allergic symptoms such as asthma or rhinitis are often due to specific IgE antibodies to environmental allergens.^{1,2} Less clear-cut evidence exists for the role of these antibodies in food intolerance and various dermatoses, although a causal relation has been established in certain cases.³

These specific antibodies have been measured by the radio-allergo-sorbent test (RAST) for several years,⁴ and there is much evidence that, particularly with respiratory allergens, the incidence and strength of the antibodies correlate well with the diameter of the wheal-and-flare reactions following prick or scratch skin tests but not with cutaneous reactions to dietary allergens.

The value of measuring specific IgE antibodies in the diagnosis and practical management of allergic disease is not clear. Indeed, the tests have been said to have little place in routine clinical immunology laboratory services.^{5,6} Often they provide only confirmatory evidence of specific hypersensitivity already recognised on clinical grounds (including skin tests).

Nevertheless, there is considerable pressure on laboratories to provide these tests to assist clinicians, especially in the management of young children with allergic symptoms, patients with severe eczema or dermatoses, patients in whom gastrointestinal allergy is suspected, or those in whom skin testing may be contraindicated or unreliable. The pressure also stems partly from a lack of understanding of the modern concepts of allergy, since many examples of sensitivity may be the result of idiosyncratic reactions (e.g., aspirin angio-oedema), in which there is no evidence of the participation of IgE-mediated mechanisms.

To assess the usefulness of RAST tests in the management of patients with putative allergic symptoms referred for consultant opinion, a study was conducted from December, 1980, to November, 1981.

PATIENTS AND METHODS

Study Design

Ten consultants (five adult chest physicians, two ear, nose and throat [ENT] surgeons, and three paediatricians) agreed to participate and to refer patients for analysis. In addition, there were 26 patients with a variety of symptoms thought to be allergic who were directly referred to one of us (R. A. T.), and 6 who had been referred to a dermatology clinic for urticaria or eczema thought to be due to food allergy.

The method of referral was to send a serum specimen and a proforma giving details of symptoms, treatment, and results of skin tests where available, as well as the usual patient identification information.

Each serum sample was tested for total IgE level and for specific IgE antibodies against a panel of nine allergens (see table III). In the summer months, an extract of the weed plantain was substituted for the mould alternaria. The range was chosen as representing the most commonly occurring sensitivities in the U.K.⁷ Patients referred specifically because of dermatological or gastrointestinal allergies were not tested against moulds. In addition, when patients gave a history of specific sensitivity to a particular allergen not included in the standard panel, serum was sent for specific IgE testing to the Allergy Unit, Benenden Chest Hospital, Kent, if an appropriate reagent for it was available.

Assays were performed every 1 or 2 weeks, and the results were passed on immediately to the clinicians to enable them to use the information in the management of their patients. At the end of the study the clinicians were asked to indicate, from a retrospective consideration of the patient's progress, whether the information provided was useful, and whether it influenced their management. For a number of reasons, this information was not available for all 301 patients whose sera were tested.

METHODS

Specific IgE antibodies were measured by the use of standard RAST kits (Pharmacia). Results were graded as negative (grade 0) or positive (grades 1-4) by comparison with a reference standard antibody to birch pollen antigen on reference discs.

Total serum IgE was measured by the radioactive single radial immunodiffusion test.⁸ Levels below 100 IU/ml were measured by a double antibody technique with competitive inhibition of precipitation of ¹²⁵I-labelled IgE, by the use of a Kallestad kit.

RESULTS

There were 168 males (average age 20.4 years, range 9 months-59 years) and 143 females (average age 22.5 years, range 11 months-59 years). 17% of the patients had specific IgE antibodies to three or more of the antigens in the panel, 37% were positive to one or two antigens, and 46% were negative to the range of antigens tested. Skin test results were available for approximately 60% of patients. In 76% of these results of the RAST correlated well with skin tests. Most (12) of the rest had a positive RAST test and a negative skin test. All but 2 of these 12 showed a positive RAST against only one food antigen.

RAST positivity in the serum also correlated well with IgE levels (table I). The upper limit of normal for IgE in "non-atopic" subjects was taken as 200 IU/ml (the usual mean $\pm$ 2 SD range for random blood donors includes a proportion of atopic subjects, so it is higher than it should be⁹), with appropriate adjustment for children.⁷ All 5 subjects with a normal IgE and multiple sensitivities (three or more) showed

TABLE I-CORRELATION OF RAST RESULT WITH SERUM IgE LEVELS

Serum IgE	RAST results		
	All negative	Positive (1 or 2 antigens)	Positive (3 or more antigens)
High*	18	64	56†
Normal or low	111	49	5‡
All	129	113	61

*Above 200 IU/ml for adults, with appropriate adjustment for children.
†Includes 3 sera positive for 9 allergens.
‡Skin tests positive in all patients.

TABLE II-TOTAL SERUM IgE LEVELS IN RELATION TO ALLERGIC SYMPTOMS

Symptom complex	All patients		Patients with 1 or more positive RASTs		Patients with all RASTs negative	
	No. of subjects	Mean $\pm$ SD	No. of subjects	Mean $\pm$ SD	No. of subjects	Mean $\pm$ SD
Asthma with or without rhinitis and other symptoms	143	791 $\pm$ 2701	94	1149 $\pm$ 3299	49	124 $\pm$ 78
Rhinitis alone or rhinitis with eczema and/or gastro-intestinal symptoms	106	450 $\pm$ 958	66	618 $\pm$ 1130	40	180 $\pm$ 491
Food intolerance	20	432 $\pm$ 974	12	608 $\pm$ 1213	8	339 $\pm$ 838
Others (mainly urticaria and angio-oedema)	32	142 $\pm$ 118	20	169 $\pm$ 146	12	121 $\pm$ 90

IgE levels given as IU/ml.

positive skin tests. 18 individuals had raised IgE levels, but no evidence of IgE antibodies to the allergens used. 4 had positive skin tests to respiratory allergens (including house dust and pollen), and it is possible that the failure to detect specific IgE antibodies was due to interference of IgG antibodies with the in-vitro reactions. 6 patients were from Asia or the Middle East, and parasite infestation may have been responsible for their high serum IgE levels. Of the 49 individuals with a normal IgE and positive RAST tests to one or two allergens, 26 had been skin tested, and 21 had positive skin tests correlating with the RAST test. 5 had completely negative skin tests, but in each case the RAST was weakly positive (1+) to a single food allergen and was of doubtful clinical significance.

Total serum IgE levels in relation to different symptom complexes are shown in table II. The difference between patients with asthma and those with rhinitis without asthma ($p<0.01$) was due solely to differences in IgE levels between patients with positive RAST tests. Among those with negative RAST tests, there was no significant difference in IgE levels between the two clinical groups. The differences between those with a positive RAST test and those with a negative RAST were statistically significant in each clinical group except in those with urticarial symptoms ("others"), although this was a fairly heterogeneous group; the differences were most marked in those patients with asthma ($p<0.001$), and least in patients with food intolerance ($p<0.05$).

Table III presents the distribution of the positive tests in the different symptom groups. Patients presenting with food intolerance or urticaria as their only symptoms were not tested against moulds. As expected, in both the asthma and the rhinitis group, the commonest antibodies were those to house dust mite and timothy grass pollen. The strength of the reaction to these two allergens was similar in both groups. Antibodies to cat dander were tested for in all patients in the

TABLE III—DISTRIBUTION OF POSITIVE IgE ANTIBODIES
ACCORDING TO ALLERGIC SYMPTOMS

	Patient group			
	Asthma, with or without other clinical features	Nasal symptoms (without asthma)	Food intolerance	Others (mainly urticaria or angio- oedema and non- respiratory symptoms)
Total no. patients	143	106	20	32
No. with one or more positive tests	94	66	12	20
No. with all tests negative	49	40	8	12
No. of positive tests to:				
<i>Alternaria</i>	8 (1.5)	1 (2.0)	NT	NT
<i>Aspergillus</i>	19 (2.2)	6 (1.3)	NT	NT
<i>Cladosporium</i>	12 (2.3)	4 (1.0)	NT	NT
Cat dander	41 (2.6)	18 (1.6)	NT	NT
<i>D. pteronyssinus</i>	63 (2.9)	35 (3.0)	2 (2.3)	3 (3.3)
Timothy grass pollen	61 (2.6)	36 (2.7)	1 (1.0)	5 (2.6)
Egg albumin	26 (1.3)	20 (1.3)	9 (2.4)	9 (1.3)
Milk protein	13 (1.2)	13 (1.2)	5 (3.4)	1 (2.0)
Wheat protein	28 (1.3)	25 (1.1)	8 (1.4)	2 (1.0)
Plantain (weed)	1 (2.0)	0	NT	NT

Nos in parentheses indicate mean strength of reaction.

asthma and rhinitis groups and were less common ($p<0.05$) and weaker ($p<0.01$) in the rhinitis group.

IgE antibodies to food, especially to egg albumin, were unexpectedly common, occurring in up to 30% of each of the asthma and rhinitis groups. However, the reaction was invariably weak; in both groups the mean intensity of the reaction to egg albumin, milk protein, and wheat protein in the positive reactors was just above 1.

In contrast, subjects with food intolerance clinically had a higher incidence of positivity to these three antigens (45% to egg, 25% to milk protein, and 40% to wheat protein). Moreover, the reactions to egg and milk—a mean of 2.4 and 3.4, respectively—were stronger, but not that to wheat protein (mean of 1.4).

Although many of the food-intolerant patients with specific IgE antibodies to food antigens were clinically sensitive to egg or cow's milk or both, and benefited from a withdrawal of the antigen from their diet, this was not the case with the other groups, except for 2 asthmatic patients (1 with a weak egg antibody and 1 without) who said they thought their symptoms were worse when they had eaten egg-containing foods. Egg and/or milk were withdrawn from the diet for a trial period in 5 rhinitis patients with either or both antibodies. Only 1 seemed to benefit, although it is not possible to draw conclusions from such a small number.

Patients with rhinitis and/or asthma were also asked whether they had other symptoms which might have an allergic basis. These included eczema and gastrointestinal symptoms such as oral ulceration, abdominal pain, nausea and vomiting, and diarrhoea. These sets of symptoms have been associated with IgE antibodies to foods,¹⁰ and thus the positive specific IgE antibodies in the groups were further

TABLE IV—DISTRIBUTION OF POSITIVE IgE ANTIBODIES IN
DIFFERENT GROUPS OF PATIENTS WITH RESPIRATORY SYMPTOMS

	Patient group					
	Asthma (with or without rhinitis)			Nasal symptoms (without asthma)		
	Alone	With GI symptoms	With eczema	Alone	With GI symptoms	With eczema
Total no. of patients	93	24	26	64*	16	26
No. with one or more positive tests	29	7	12	22	6	10
No. with all tests neg.	34	11	5	24	7	9
No. of positive tests to:						
<i>Alternaria</i>	7 (1.7)	1 (1.0)	0	1 (2.0)	0	0
<i>Aspergillus</i>	13 (2.2)	1 (1.0)	5 (2.4)	5 (1.6)	1 (1.0)	0
<i>Cladosporium</i>	8 (2.1)	0	3 (2.3)	1 (1.0)	1 (1.0)	1 (1.0)
Cat dander	25 (2.3)	3 (2.7)	12 (3.2)	7 (1.7)	3 (1.3)	9 (1.8)
<i>D. pteronyssinus</i>	39 (2.7)	7 (2.9)	14 (2.8)	18 (2.8)	5 (3.0)	7 (3.1)
Timothy grass pollen	36 (2.5)	6 (2.8)	11 (2.6)	20 (2.9)	6 (3.0)	7 (2.3)
Egg albumin	18 (1.2)	3 (1.0)	6 (1.3)	9 (1.0)	2 (2.5)	7 (1.3)
Milk protein	10 (1.2)	1 (1.0)	2 (1.0)	9 (1.1)	3 (1.7)	1 (1.0)
Wheat protein	14 (1.1)	5 (1.6)	10 (1.2)	15 (1.2)	3 (1.0)	6 (1.3)

Nos in parentheses indicate mean strength of reaction.

*Includes 4 patients who were negative to the respiratory allergies but positive to a single food allergen.

analysed according to the presence or absence of these associated symptoms. The results are shown in table IV.

Sera from patients with eczema and asthma were less often negative to all the test allergens ($p<0.02$) but more often positive to one or more foods ($p<0.05$) than either those with asthma alone or those with asthma and gastrointestinal symptoms. However, there were no significant differences between the groups in the mean level of the positive response to any of the food antigens. Patients with eczema showed no significant differences in the levels of positive responses to other common respiratory allergens, except for cat dander, to which their incidence and strength of antibodies were greater ($p<0.01$) than those in patients with asthma alone or asthma with gastrointestinal symptoms.

The differences between the groups of rhinitis patients were not statistically significant.

Where it was possible to assess whether knowledge of specific IgE antibodies affected management, the respiratory physicians dealing mainly with adults found it was not crucial in the great majority (93%) of cases. The assay did not add anything to the history, the skin test results, and other clinical and laboratory information. The tests were considered most useful by chest physicians in the management of asthma patients with allergic aspergillosis, and in special cases. The

ENT surgeons found the RAST results helpful in about 40% of cases, often in those with negative skin tests (as a confirmatory measure), or in patients in whom skin tests could not be done. The paediatricians also found the tests gave information that helped in the management of about 45% of their cases. This was because of the difficulty of performing skin tests in children, or in their interpretation. 14 serum samples were sent for specific IgE antibody tests for additional allergens not in the standard panel, but except for three instances of bee and wasp venom sensitivity, the results did not help in the clinical management of the patients.

DISCUSSION

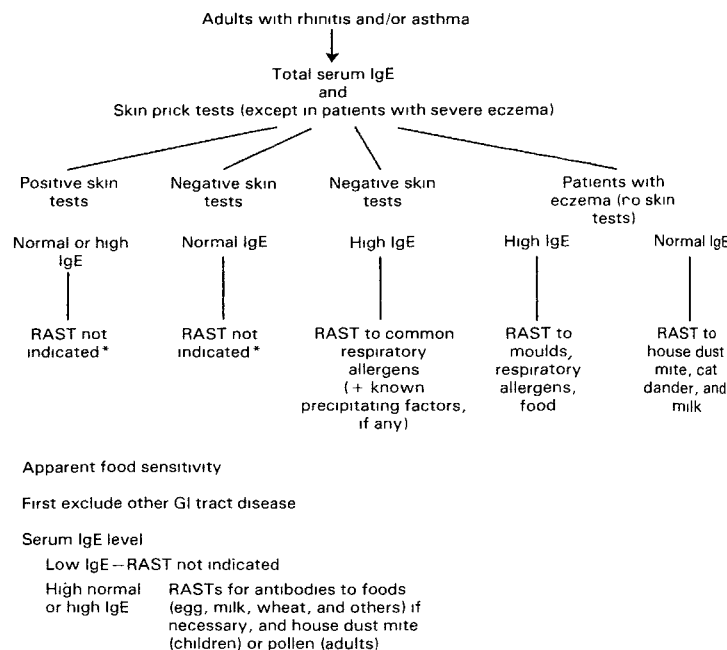
This study makes it clear that in the practical management of acute allergic symptoms, as in most other fields of medicine, the laboratory is best used as an adjunct to and not as a substitute for, sound clinical practice and judgment. When acute symptoms are due to extrinsic agents, the nature of the agent can usually be determined from the clinical history and skin tests. The management of the patient is then determined by allergen avoidance and pharmacological blockade of effector mechanisms. Specific hyposensitisation may help in some cases, but in general it is unrewarding.¹¹

In those who are sensitive to agents of which they are not aware, and in whom skin tests cannot be done or are difficult to interpret, further laboratory investigations may be indicated. These should start with a total IgE level, since this correlates strongly with the likelihood of specific IgE antibodies, together with a limited test for RAST antibodies to a few common respiratory allergens. Patients with negative skin tests and a normal ("non-atopic") total IgE level are extremely unlikely to have specific IgE antibodies to any ubiquitous respiratory allergens that might form the basis for a rational "screening" procedure. However, since food antigens may not give positive skin tests even when specific IgE antibodies are present, individuals, especially children, with food sensitivity, may benefit from specific IgE antibody tests, provided that other gastrointestinal diseases have been excluded.

Tests for specific IgE antibodies to foods in patients with predominantly respiratory symptoms seem of little value. Our findings suggest that such antibodies are not uncommon at a low level in atopic subjects. They could be due to concomitant sensitisation or a persistence of childhood sensitisation, or possibly a cross reaction with respiratory allergens (wheat protein and grass pollen), but they seem to be of little clinical significance. Patients with asthma and eczema are more likely to have such antibodies, but again the clinical significance of these is uncertain.

Bee and wasp venom and penicillin sensitivity can occur despite a normal total IgE level and in non-atopic individuals. Tests for specific IgE antibodies or skin tests should be performed in patients giving a history of acute reactions to bee or wasp stings since hyposensitisation with purified venom may be indicated.^{12,13}

Many patients with perennial respiratory or nasal symptoms or spontaneous urticaria and angioneurotic oedema do not seem to have an IgE mediated mechanism as the underlying cause. Their symptoms may be due to homocytotropic antibodies of other immunoglobulin classes,¹⁴ and the role of these antibodies may become clearer when reagents for the determination of such specific antibodies become more widely available. Alternatively, the symptoms may be due to the action of other specific hypersensitivity mechanism as yet undetermined; or they



Investigation of patients with allergy.

RASTs could still be done if there were special circumstances—e.g., strong history of particular provoking allergen, or difficulty in management, or for allergic aspergillosis, or difficulty in interpreting skin tests, or in children in whom skin tests could not be done.

Bee and wasp venom RASTs available independent of IgE level.

may be the result of disorders of effector mechanism regulation that are not yet understood. The routine clinical laboratory is, however, only able to offer limited assistance in determining specific IgE antibodies at the present time.

The RAST test is time consuming and expensive of reagents and, if offered as a service in the N.H.S., it should not be used as a "screening service"; hence some constraints should be placed on its availability. The accompanying figure suggests a scheme for the use of specific IgE antibody tests in the investigation of patients with allergy. It would considerably reduce the costs of having such a service whilst still allowing the greatest yield of information from RAST analysis in patients with acute allergic symptoms.

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REFERENCES

- Wide L, Bennich H, Johansson SGO. Diagnosis of allergy by an in vitro test for allergen antibodies. *Lancet* 1967; ii: 1105-07.
- Gleich GJ, Jacob GL, Yunginger JW, Henderson LL. Measurement of absolute levels of IgE antibodies in patients with ragweed hay fever: Effect of immunotherapy on seasonal changes and relationship to IgE antibodies. *J Allergy Clin Immunol* 1977; **60**: 188.
- Wraith DG, Merrett J, Roth A, Yman L, Merrett T. Recognition of food allergic patients and their allergens by the RAST technique and clinical investigation. *Clin Allergy* 1979; **9**: 25-36.
- Wide L. Clinical significance of measurement of reagenic IgE antibody by RAST. *Clin Allergy* 1973; **3** (suppl.): 583-93.
- Reeves WG, Marrott DW. Radioisotope techniques. In: Thompson RA, ed. *Techniques in clinical immunology*. Oxford: Blackwell Scientific Publications, 1981: 138-56.
- W H O/I U.S. Working Group Report: Use and abuse of laboratory tests in clinical immunology: critical considerations of eight widely used diagnostic tests. *Clin Exp Immunol* 1981; **46**: 662-74.
- Merrett T, Pantun CFA, Dimond AH, Merrett J. Screening for IgE-mediated allergy. *Allergy* 1980; **35**: 491-501.
- Rowe DS. Radioactive single radial immunodiffusion: A method for increasing the sensitivity of immunochemical quantitation of proteins in agar gel. *Bull WHO* 1969; **40**: 613-16.
- Spitz E, Gelfand EW, Sheffer AL, Austen KF. Serum IgE in clinical immunology and allergy. *J Allergy Clin Immunol* 1972; **49**: 337-47.

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Occasional Survey

IS SCHIZOPHRENIA AN INFECTIOUS DISEASE?

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Summary The role of genetic predisposition in schizophrenia is undoubted but some of the data on family concordance cannot be explained on the basis of genes alone: for instance, the concordance rate is higher in same-sex than in different-sex dizygotic-twin and sibling pairs and in same-sex dizygotic twins than in same-sex sibling pairs. The findings can be understood if disease expression is also a function of physical proximity to an affected individual, as is suggested by the fact that the anomalous findings occur within primary but not secondary family relationships. There is some familial and epidemiological evidence to support the hypothesis of transmission from affected to non-affected individuals. Schizophrenia could be due to a virus which is transmitted predominantly from schizophrenic patients to genetically-predisposed individuals, perhaps in some cases with a latency of approximately six months.

INTRODUCTION

CONCORDANCE rates in twins for schizophrenia are between 35% and 58% for monozygotic pairs and between 9% and 26% for dizygotic pairs.¹ This finding strongly suggests a genetic component, but the extent to which concordance in monozygotic pairs falls short of 100% and the adult onset of the disorder emphasise that schizophrenia is not a simple inherited disorder of metabolism. Adoption studies also suggest a genetic influence: the rates of schizophrenia in children of schizophrenic patients brought up by unrelated adoptive parents are higher than the population incidence,² and an excess of schizophrenia is found in biological, by comparison with adoptive, relatives of adopted children who later become schizophrenic.³ It is puzzling that a disease which is known to reduce fertility remains so prevalent.⁴

THE VIRAL HYPOTHESIS

Schizophrenia could be caused by a virus. Schizophrenia-like symptoms were seen in association with the influenza epidemic of 1918,⁵ Vilyuisk encephalitis,⁶ and encephalitis lethargica,⁷ which is presumed to be caused by a virus. Compatible with a viral aetiology is a tendency toward a seasonal distribution. There is a season-of-onset effect—illnesses are more likely to present in early summer

than at other times of the year⁸—and a season-of-birth effect—patients who become schizophrenic are more likely to have been born in the winter months than at other times.^{8,9} A similar phenomenon occurs in Japanese encephalitis; patients born at certain times of the year are more susceptible to the disease and more resistant to immunisation.¹⁰ In this disorder the effect is attributed to the induction of tolerance by early exposure to the antigen in seasonal epidemics.

A difficulty with a viral hypothesis is the lack of evidence that schizophrenia is transmitted from one individual to another. Even if susceptibility were confined to a genetically predisposed subpopulation and even if a latent period were involved, some evidence that disease onset is related to contact with schizophrenic individuals would be expected. This report draws attention to data from familial and epidemiological studies compatible with person-to-person transmission.

ANOMALIES IN GENETIC EVIDENCE

Two findings in family studies cannot readily be explained on a genetic basis. First, concordance rates for pairs of relatives are consistently higher for pairs with both members of the same sex than for pairs with members of different sexes.¹¹ This excess was found in three studies of dizygotic-twin pairs (table I) and in four studies of sibling pairs (table II). Therefore, in both dizygotic twin pairs and sibling pairs concordance rates are higher when the pair members are of the same sex. This relationship can be examined in pairs of relatives extending beyond a single generation, both within and outside the immediate family, in Penrose's 1942 report of 500 male and 500 female patients admitted consecutively under certificate to the Ontario Hospital. Relatives were classified in each case as to whether they were known to have suffered from psychosis. The data can be analysed by sex and by whether the relationship is primary (i.e., within the immediate family) or secondary (outside it). The excess of same-sex over different-sex pairs is highly significant in the primary relationships, but there was no apparent excess in secondary relationships (table III).

The second anomaly relates to the fact that dizygotic twins and siblings share genes to the same extent and by simple genetic theory would be expected to have similar concordance rates. Fischer²⁰ carefully collected the psychiatric histories of siblings of 45 dizygotic-twin pairs of whom at least one was schizophrenic and compared concordance rates for same-sex twin pairs with those for their same-sex siblings. There is a highly significant excess of concordances in the dizygotic-twin pairs (12 of 45 *vs* 13 of 129 same-sex sibling pairs; $p=0.0062$ by Fisher's test). These familial concordances cannot be explained on a purely genetic basis. On the contrary, they are consistent with the possibility that what matters is physical proximity. Same-sex pairs of siblings are likely to be in closer contact (for example, by sharing a bedroom) than different-sex pairs. The excess of cases over the numbers expected on genetic lines occurs within the family unit (primary relationships) rather than outside it. Dizygotic-twin pairs, because of their age, are likely to be in closer physical proximity with each other than with their siblings.

EVIDENCE FOR TRANSMISSION

If genes predispose to a disorder, the population at highest risk consists of the monozygotic co-twins of proband twins in whom the disorder has already developed. The time of onset

R. A. THOMPSON AND A. G. BIRD: REFERENCES—continued

- 10 Brostoff J, Carini C, Wraith DG, Johns P. Production of IgE complexes by allergen challenge in atopic patients and the effect of sodium cromoglycate. *Lancet* 1979; *i*: 1268-70.
- 11 Morrison Smith J. The treatment of allergic disease. In: Thompson RA, ed. *Recent advances in clinical immunology*. Edinburgh: Churchill-Livingstone, 1977: 271-92.
- 12 Miyachi S, Lessof MH, Kemeny DM. Evaluation of bee sting allergy by skin tests and serum antibody assays. *Int Arch Allergy Appl Immun* 1979; **60**: 148-53.
- 13 Hunt KJ, Valentine MD, Sobokte AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1979; **299**: 157-60.
- 14 Parish W. A human heat-stable anaphylactic or anaphylactoid antibody which may participate in pulmonary disorders. In: Lichtenstein L, Austen KF, eds. *Asthma*. New York: Academic Press, 1973: 71-90.