Sixties Clinical

CF Centre care for a few people in some countries - both benefits and side effects from long term treatment

A review of management presented to the American Academy of Pediatrics in 1958 by Harry Shwachman, the most experienced CF clinician at the time, who urged caution “against discarding any form of therapy that offers relief” but avoiding “the use of harmful agents and needless operative procedures”. The article is a pleasure to read and full of wise advice. For example, he stressed the importance of early and certain diagnosis, adequate education of the parents, seeing the patient at regular intervals, also being readily accessible for advice. On the last he comments - “clinic as well as private patients may call us on the phone whenever questions arise”. Although often accused of advising severe fat restriction, Shwachman states that fat is allowed as tolerated. Iodides were thought to be helpful in thinning the viscid secretions, intramuscular or aerosol pancreatic trypsin were not recommended nor were carbon dioxide inhalations but the mist tent, with a 10% solution of propylene glycol and 3% saline, was helpful as were “English” methods of physiotherapy. Antibiotics were central to treatment but the parenteral route was rarely used – a major difference to present day treatment. Oral chlorotetracycline or oxytetracycline, at times were combined with erythromycin or a sulphonamide, and aerosol penicillin and streptomycin or neomycin and polymyxin.

It is interesting, in view of the present role of macrolides, that both Harry Shwachman and Margaret Mearns appeared to find erythromycin was helpful.

Charlotte Anderson (from Melbourne and later Birmingham UK) showed no abnormality in the sweat electrolytes from parents or siblings of people with CF nor in patients with other chronic chest diseases. A wide scatter of results was obtained in adults for example 34/100 normal adults had sweat sodium levels over 60meq/l. Anderson states that “determination of sweat sodium and chloride loses much of its value” in adults. Also intradermal mecholyl chloride was used to stimulate sweating in Anderson’s study.

This method of stimulating sweating did not become popular and we heard of one serious reaction with the method. The details of the methods used in the study were criticised by di Sant’Agnese as a different dose of mecholyl was used in the different age groups and this may have affected the rate of sweating which would influence the concentration of electrolytes (also Simmonds EJ, et al. Arch Dis Child 1989; 64:1717-1720. [PubMed] ). di Sant’Agnese considered that the conclusions drawn by Anderson and Freeman “were not warranted by their limited experience”. Fortunately during the Sixties the sweat test by the Gibson and Cooke pilocarpine iontophoresis method, first described in 1959 (above), slowly became the gold standard. Later studies from Great Ormond Street, London (McKendrick et al, 1963 below) showed the sweat electrolytes were insignificantly higher than normal in obligatory heterozygotes.

A very detailed report from Melbourne of a middle aged man with long standing bronchial infection, bronchial damage and chronic diarrhoea with pancreatic achylia determined by detailed pancreatic function tests. The sweat sodium and chloride were 85 and 71 meq/l respectively. Spermatozoa were absent from the seminal fluid. There was a family history of deaths in middle and older age from chronic lung disease. A very detailed report from Melbourne of a middle aged man with long standing bronchial infection, bronchial damage and chronic diarrhoea with pancreatic achylia determined by detailed pancreatic function tests. The sweat sodium and chloride were 85 and 71 meq/l respectively. Spermatozoa were absent from the seminal fluid. There was a family history of deaths in middle and older age from chronic lung disease.

This was the oldest well-documented patient reported up to this time – with very convincing evidence for the diagnosis.

This article is confusing. The writer discusses the possibility of encountering CF in older patients and mentions the Marks & Anderson case (Marks & Anderson, 1960 above). Also there is discussion of a paper by Koch of Giessen (Koch E. Germ med mon 1960; 5:40) who searched for CF in an adult hospital population and reviewed “84 such cases” – presumably considered to have cystic fibrosis. He searched through healthy students, gall bladder patients, peptic ulcer patients, 88 patients with unrelated complaints and 68 close relatives of CF patients. Diagnosis was based on sweat tests and pancreatic enzymes in duodenal aspirates - the activities of one or more were
However, the findings of this particular study of Koch’s are difficult to accept. For example “of the 68 relatives of 41 cases of mucoviscidosis only 9 were free from symptoms, signs or laboratory evidence of the disease”. Also an article from the same author in 1959 entitled “Mucoviscidosis in adults, a very frequent dominant hereditary disease” (Bohn H Koch E. Die Mediz 1959; 4:1139-1149) does little to reassure one that the findings in the present paper are valid. Subsequent studies searching for undiagnosed CF in populations of patients with bronchiectasis and chronic bronchitis did not reveal patients with unrecognised cystic fibrosis (Muir et al, 1962 below). Although the findings in this paper are questionable when viewed in the light of subsequent publications, the possibility of encountering this new disease – CF – was being suggested to clinicians dealing with adults and other gastrointestinal and respiratory conditions.


Increased levels of gamma globulin, as determined by paper electrophoresis reflected the severity of the pulmonary disease. Subsequent studies confirmed the relationship of high immunoglobulin levels with severe chest involvement. The levels correlated with disease activity (Matthews WJ et al. N Eng J Med 1980; 302:245-249); also a subgroup of children with lower immunoglobulin levels appeared to have a better prognosis when followed over 5 years (Wheeler WB et al. J Pediatr 1984; 104:695-699 below). Also later more specific qualitative immunoglobulin abnormalities were reported as characteristic of the condition such as low IgG2 (Garside et al, 2005; Garside et al, 2007 both below)


The authors became aware of complaints referable to impaired vision and abnormal fundal appearances in their patients in the summer of 1958 and they report the eye findings in 27 patients. Definite impairment of vision was noted in 4 of 10 patients. Characteristic findings were “varying degrees of engorgement and edema of the disc marked in some instances by haemorrhages and in others by cystic changes in the macula”. All those affected had severe pulmonary involvement and raised gammaglobulin levels in the serum and spinal fluid. A later report failed to provide an explanation for the eye changes possibilities including chronic hypoxia, hypercapnia, right heart failure, increased intracranial pressure, a bleeding tendency or some disturbance of serum globulins (Soc Pediatr Res 1960; abstract 127). In 1963 the effects of chloramphenicol were reported (Denning et al, 1963 below).

Dr Carolyn Denning was one of the leading CF paediatricians at that time working first in New York with Dorothy Andersen and later at St Vincent’s Hospital in New York. In the figure 5 she is examining the hand print of a person with CF on a “Shwachman plate” (see N Eng J Med 1956:255:999-1001 above). I had the pleasure of visiting her unit in the late Eighties, having been encouraged to do so by Ron Tucker the then Director of the UK CF Trust; he was very keen that I should visit her. Carolyn Denning was the first woman to chair the National Cystic Fibrosis Foundation’s Medical Advisory Council and was one of the first to organize and initiate a multidisciplinary team approach to management of the disease – this was very apparent when I visited her and her team at St Vincent’s, New York. A quote from the website “A Changing Face of Medicine” typifies her general approach - "My office visits," she says, "are conducted in a private setting with no interruptions by telephone or office personnel with a one-hour minimum allotted to each patient. I am realistic yet optimistic, stressing the importance of hope. I am current on research activities in the field as well as other important relevant events. I follow through on all matters pertaining to the patient and his office visit and I am available by telephone at all times. I put great stress on personal integrity, ethics and moral beliefs. As director of a large, multi-disciplinary group of health professionals, I have worked hard to choose people who share the same philosophy.” It was good to see such an excellent team in action.


Jean Feigelson (figure 6) of Paris is one of the pioneers of CF care and still, in 2009 attending CF conferences in Europe and North America. He trained in paediatrics at the Sick Children’s Clinic in Oslo in 1952. In a career spanning over 45 years he has treated over 250 people with cystic fibrosis. This is Jean Feigelson’s first recorded paper on cystic fibrosis. His most recent is as a co-author of a paper on partial splenectomy, that was published in 2007 (Louis D et al, Pediatr Pulmonol 2007; 42:1173-1180). He has 48 references noted in Medline produced steadily over 40 years.

This was the first report of pregnancy in a lady with CF; the patient died six weeks after the birth. The authors concluded, “cystic fibrosis is seriously complicated by pregnancy”. As the survival and condition of patients with CF improved, an increasing number of women with CF had successful pregnancies (Cohen et al, 1980 below; Gilliam et al, 2000 below; Edenborough et al, 2000 below), even some who had undergone lung transplantations (Gyi KM et al. J Cyst Fibros 2006; 5:171-175).

This is the first report of per oral duodenal biopsy in 17 children with coeliac disease; 11 of whom were re-biopsied after taking a gluten free diet when all had improved histology. Eventually it would become practice, in patients considered to have coeliac disease and treated with a gluten free diet, to re-biopsy to ensure the intestinal mucosa had recovered and at some stage later to re-challenge with gluten powder to ensure the gluten intolerance was permanent before committing the patient to a lifetime gluten free diet.

This report was some three years after the first reports of per oral intestinal biopsy in adults by Margot Shiner (Sakula J, Shiner, M. Lancet 1957; ii: 876) and the first in children. It is an important paper both with regard to the management of coeliac disease and also important in improving the means of clearly differentiating between cystic fibrosis and coeliac disease; also rarely the coexistence of the two conditions could be identified (Hide & Burman, 1969 below). This recently introduced technique of per-oral duodenal biopsy permitted a positive diagnosis of coeliac disease for the first time (see comment on Samuel Gee,1888 above). The technique gradually became more generally available at major centres throughout the UK during the Sixties. Note the author of this paper is Charlotte Anderson – not Dorothy Anderson – the spelling is confused in more than one publication – even by the editor of a leading paediatric journal!!

Charlotte M Anderson (1915-2002) (figure 7) was the first woman to be appointed a Professor of Paediatrics in the United Kingdom. She qualified in 1945 and after hospital jobs in Melbourne she worked at the Hospital for Sick Children at Great Ormond Street, London and at the Institute of Child Health at the University of Birmingham. Her work with British colleagues on the role of gluten in coeliac disease (Anderson CM et al. Coeliac disease gastrointestinal studies and the effect of wheat flour. Lancet 1952; i: 836-842) was carried out at much the same time as that of Dicke and colleagues in Holland, and helped to establish her international renown. She started the first Australian cystic fibrosis clinic in 1953 in Melbourne and published widely on both CF and paediatric gastroenterology. She became Professor of Paediatrics at the University of Birmingham and director of the Institute of Child Health in 1968. I was fortunate to hear her speak at the Samuel Gee, 1988 Coeliac Centenary Meeting at St Bartholomew’s in London and to talk with her and Margot Shiner (the first person to perform per oral intestinal biopsy) over lunch time sandwiches! 1960 Young WF.

1960 Young WF. Ototoxicity to neomycin aerosol. Lancet 1960; i: 1103.
This letter to the Lancet from Winifred Young (1909-1969) (figure 8), of the Queen Elizabeth Hospital for Children, London, followed closely a report from the Royal National Throat, Nose and Ear Hospital, London, of two children with CF who had received nebulised neomycin for 34 months and 26 months respectively and who had become severely deaf (Fuller A. Ototoxicity of neomycin aerosol. Lancet 1960; i: 1026). Winifred Young responded that the patients were part of a series of children treated at her CF clinic at the Queen Elizabeth Hospital for Children, London and both the children had very severe chest involvement – in fact, both had since died. Dr Young and her otological colleagues “had been able to reassure herself that neomycin aerosol can be used for many months without risk of ototoxicity”. Despite this reassurance, the use of long term nebulised neomycin was eventually abandoned due
to otoxicity – at that time it was not appreciated that inhaled antibiotics could be absorbed in significant amounts. Inhaled neomycin was first described as a treatment for CF in 1956 (Gibbs GE & Raskin J. Antibiotic Med Clin Therapy 1956;2:332-336). A case report of otoxicity appeared in 1959 (Greenwood GJ. AMA Arch Otolaryngol 1959; 69:390-397) and in a number of reports in the early Sixties although most reports of otoxicity and CF concern the aminoglycosides.


This report is to two children with CF who developed hypothyroidism whilst taking iodide therapy to improve sputum clearance – in these two patients there was no thyroid enlargement. Later Dolan TF & Gibson LE (J Pediatr 1971; 79:684-687) reported 55 patients on long term iodide therapy of whom a remarkable 85% developed goitres and also 24% had evidence of hypothyroidism. Their thyroid glands were enlarged, sometimes markedly so, usually after three years or so of iodide therapy. There was discussion as to the possibility of an intrinsic defect of thyroid function but people with CF not taking iodies were all euthyroid.


There were severe discoloration of the teeth in 38 of 52 children and adolescents with CF. In 31 the deciduous teeth were involved, the permanent teeth in 18 and both in 11. The authors noted that tetracycline had been involved in animals and speculated that antibiotic therapy “might conceivably contribute to the discoloration by deposition in the teeth”. In 1959 Shwachman et al. had recognised tooth staining (Antibiot Ann 1958-1959, 692-699) (figure 20 in Shwachman et al, 1958 above). Subsequently Zegarelli, usually with Carolyn Denning of New York, published 11 papers on tooth discoloration. Tetracycline is deposited in growing bone and teeth by complexing with the bone mineral (Witkop CJ, Wolf RO. JAMA 1963; 185:1008-1011). Subsequently tetracyclines were avoided in children under seven years of age and also by pregnant women.

The dangers of some drugs taken by the mother during pregnancy were becoming apparent at this time - particularly the thalidomide tragedy which came to light in the early Sixties after over 10,000 infants had been born with various limb deformities between 1956 and 1962 as a result of their mothers taking the drug during pregnancy.


The incidence of hepatic cirrhosis varies in different reports but all agree the complication increases with age. In 200 people with CF, “cirrhosis” occurred in 1% aged less than 3 months, 6% between three and 12 months, 11% one to three years, 37% over three years of age. Histologically there was a focal biliary cirrhosis, diffuse multilobular cirrhosis and/or portal hypertension. The lesson the authors took from their findings was that “Investigation of the young cirrhotic patient is incomplete without a sweat test” – which is still sound advice today.


These authors screened 250 adults with diabetes mellitus using Shwachman plates (Shwachman et al, 1956 above) and those who were positive had sweat tests performed by the bag method. Nine of the 250 diabetic adults had positive sweat tests but no other signs of cystic fibrosis. These findings are difficult to explain, and indeed accept, as diabetes mellitus is usually a late feature in the progression of cystic fibrosis. Also the ages of the patients (between 49 and 66 years) were quite against their having cystic fibrosis. It is difficult to accept these findings particularly as there were no other signs of cystic fibrosis in these middle aged patients. Also a number of authors had found some apparently healthy adults with sweat tests with values of sodium and chloride over 60 meq/l. This paper was followed by a number of publications on the relationship between established diabetics and cystic fibrosis. The first description of diabetes mellitus in cystic fibrosis is usually attributed to Shwachman & Leubner, 1955 (above).


The authors managed to perform pilocarpine iontophoresis sweat tests in the first four days of life in 37 babies - a difficult feat at this early age. Another six newborns with intestinal obstruction were tested – the four with CF were all sweat test positive and the two with negative sweat tests had respectively Hirschprung’s disease and ileal atresia. So sweat tests were already positive in the newborn period in infants with CF but an experienced and skilful technician would be required to perform the investigation. If an urgent answer is required at the present time, a check on the infant for the presence of CF mutations would be helpful in most instances.


An interesting report where Shwachman describes performance of over 2000 “bag” sweat tests – 335 in patients with CF. The mean chloride level in people with CF was 113 meq/l and mean sodium 112meq/l compared with controls’ values of 23 and 23 respectively. The bag method was abandoned in 1958 in preference to the pilocarpine method of Gibson and Cooke (1959 above) with which the bag results were compared.

1961 Kunstadter RH, Mendelsohn RS. Norethandrolone in children with and without
In 1961 as the chest infection progressed and increased in severity, it was very difficult, and usually impossible, to achieve normal weight gain and growth in children with cystic fibrosis. As the available pancreatic enzyme supplements were relatively inefficient, most patients took a low fat diet to avoid very unpleasant bowel symptoms; also there was a severe catabolic wasting effect from the active and increasingly severe chest infection. However, in this report of 14 children with CF treated with anabolic steroids there were “remarkable gains in weight”.

Shwachman commented that he had used one such preparation (Nilevar) on 30 patients and found the drug “very useful but not to be used routinely”. This was the first of a number of reports that anabolic steroids had a favourable effect on weight gain in children with cystic fibrosis. The drugs were to become quite widely used as nutritional problems became increasingly severe as more children survived for longer and nutrition continued as an increasingly significant problem. It was not until the early Eighties that there was marked improvement in the control of the intestinal malabsorption following the introduction of the acid resistant enzymes (Pancrease and later Creon); also around that time, for those with more severe nutritional problems, more aggressive nutritional interventions such as nasogastric and gastrostomy feeds, became available. So the use of anabolic steroids gradually declined (also Dooley RR et al. J Pediatr 1969; 74:95-102). The subject was reviewed in 1981 by Richard Dooley (Anabolic steroids. In 1000 years of Cystic Fibrosis. Warren Warwick (ed). University of Minnesota, 1981).

An early description of nasal polyps in cystic fibrosis (also Lurie MH, 1959 above). Of 650 patients with CF seen over the previous 4 years, 43 (7%) had nasal polyposis - 10% of those over 3 years. The effect on facial appearance, increasing the width of the nasal bridge, and the tendency to recur after removal were stressed. There was nothing characteristic about the histological appearance of the polyps. A sweat test was recommended in any child with nasal polyposis.


Later more accurate assessment of the incidence of polyps was possible that 37% of patients were affected. Inhaled steroids were used with some success as local treatment – eventually many years later confirmed in a controlled trial (Hadfield et al, 2000 below). Also as an incidental finding during a trial of oral ibuprofen for the chest infection, the nasal polyps were observed to shrink (Lindstrom et al, 2007 below).

This is said to be the first randomized controlled trial in people with cystic fibrosis. A double blind placebo controlled parallel single centre randomised controlled trial in which the effect of tocopherol supplementation on muscle strength was evaluated, by means of a “hand bulb ergograph” which was squeezed to measure grip strength. There was no difference in strength noted with vitamin E supplementation – both the treated and placebo group improved.

Oppenheimer had been the first to report an infant with necrotic changes in muscle resembling those found in tocopherol deficiency (Oppenheimer. EH. Bull Johns Hopkins Hosp 1956; 98:353-358). The authors of the present studies concluded that “although the present study did not demonstrate a clinical functional effect of tocopherol therapy in patients with cystic fibrosis, its administration is recommended because of previously reported biochemical and pathological evidence of vitamin E deficiency in these subjects”. This very reasonable approach would be a lesson for some clinicians who would not use a treatment unless supported by a suitable randomised controlled trial - a view I have even heard expressed with regard to vitamin E supplements in CF! Here all the available reasonable information was considered before a policy was recommended that may well do good and was very unlikely to do harm to their patients.

There was a fall in serum albumin from 4.0 to 2.6 g/dl over 30 days in an infant with CF fed a soy formula. The normal half life of 131I-labelled albumin excluded an exudative protein loosing enteropathy. The authors suggested that in CF infants soy protein absorption is more affected than cow’s milk protein.

Usually serum albumin is, rather surprisingly, within the normal range in CF unless there is significant liver involvement. However, it became apparent in a number of subsequent reports that soya based milk preparations were particularly likely to be associated with hypoproteinaemia in infants with cystic fibrosis (Fleisher et al, 1964 below; McClean &Tripp, 1974 below; Lee et al, 1974 below).

One of the early descriptions of diabetes mellitus in cystic fibrosis; the first was in 1955 in an article by Shwachman & Leubner (above). In the present paper 10 patients with diabetes mellitus...
were identified in a CF population of about 1300 patients seen since 1947 - one adult, three teenagers and the rest children. Reviewing the 10 patients – eight required insulin therapy, they noted that diabetes complicates management but does not necessarily shorten survival; it may begin at any age; four of the 10 patients were mentally retarded – an unusual occurrence in CF which was not discussed; the complication was indistinguishable from juvenile diabetes except ketosis was very rare; all were completely pancreatic insufficient. The authors predicted that subclinical diabetes must exist in a large proportion of people with CF. This prophetic observation was absolutely correct but was a new concept at the time when there were very few adults with cystic fibrosis. There were so few patients with diabetes mellitus and CF that this paper reporting 10 patients was published.


One hundred adults with chronic bronchitis, 42 patients with other chest diseases and 25 controls were screened with the fingerprint method for raised chloride levels in the sweat (method of Shwachman & Gahm, 1956 above). None of the patients had excessive sweat chloride levels as judged by the plate test and the authors concluded that cystic fibrosis, in the homozygous state, could not be implicated as a cause of their chronic bronchitis.

It was reasonable to search for people with CF amongst those with similar chronic disorders. As in the present study, usually there were no patients with CF amongst the patients studied. Later this group, at the Royal Brompton Hospital in London, also failed to find an increase in respiratory disease amongst obligate heterozygotes for CF – that is to say the parents of people who had cystic fibrosis (Batten et al, 1963 below).


A study by Dr Tom McKendrick, a senior registrar working at Great Ormond Street, London with Dr (now Dame) Barbara Clayton, the chemical pathologist, and Dr Archie Norman, using the recently described Gibson and Cooke pilocarpine iontophoresis method of sweat stimulation (Gibson & Cooke, 1959 above). In normal children sweat sodium was almost always less than 60 meq/l rising from 22 to 44 in the first 14 years and rising to 55 in adults. 95% of people with CF had sodium levels over 70 and parents and siblings showed levels slightly greater than normals. The levels were normal in chronic bronchitis patients i.e. there were no people with CF amongst those considered to have chronic bronchitis. The conclusion was that the “The wide variation of results both in single subjects and within groups of similar subjects limit the value of the test. It is useful only for confirming the diagnosis of cystic fibrosis” – for which, of course, it proved of immense value and to be a major advance, eventually becoming the “gold standard” method of sweat testing.


This report, often incorrectly quoted as first description of meconium ileus equivalent, describes the condition in a boy aged 15 years – however, it was the first time the term “meconium ileus equivalent” was used. Already Levy (1951 above) and Fischer (1954 above) and others had reported post neonatal intestinal obstruction. Also Fanconi (Helvet Paediat Acta 1960; 15:566-579) had used the term “post-neonatal meconium ileus”. This present patient of Jensen’s had an ileostomy through which pancreatin was infused which relieved the obstruction.


First description of gall bladder abnormalities noted at autopsy that were present in 24 of 72 people with cystic fibrosis. “The cystic duct may be atretic or stenotic from inspissated mucus or mucosal hyperplasia. Mucus distends the gallbladder epithelial cells and fills the lumen with a colourless secretion. The gallbladder may atrophy or persist as a thin walled cyst lined with flattened mucosa”. Radiological appearances of the gall bladder and bile ducts had been reported by Jones et al, 1958 (above).


In this publication Dorothy Andersen reported that the lungs of CF infants were normal at birth. Others agreed that the lungs were “essentially normal” at birth (Zuelzer WW & Newton WA. Pediatrics 1949; 4:53-59. [PubMed] However, others later found that there is an accumulation of mucin in the tracheobronchial glands of the fetus with CF even in the second trimester (Ornony A et al. Am J Med Genet 1987; 28:935-947 ); [PubMed] and in the post natal period, even before infection occurs, changes are present in the submucosal glands (Oppenheimer EH, Esterly JR. Perspect Pediatr Pathol 1975; 2:241-278).[PubMed]. Under four months of age there is some slight dilatation of the acini of the tracheal submucosal glands but gland development and architecture are normal (Sturgess J, Imrie J. Am J Pathol 1982; 106:303-311). [PubMed] Despite these findings, which lead to very slight hyperinflation of the lungs, for practical purposes the respiratory function is normal and can be maintained in a stable state with little of no deterioration for many years provided chronic infection can be prevented by early diagnosis, careful microbiological monitoring and aggressive antibiotic treatment.


Acetyl cysteine, a derivative of the amino acid cysteine, is a drug that subsequently was widely used for CF in Europe but never popular in the UK. Here experience is reported of 285 patients
with a variety of suppurative pulmonary conditions and "revealed it to be extremely effective with almost no associated complications. Seven patients with CF improved over 10 months with either inhalations or sleeping in a tent with the drug nebulised with saline and propylene glycol". (figure 9).


**Figure 9**: 24 hour sputum collections from a man with purulent bronchitis during the day prior to and the 4 days subsequent to use of acetyl-cysteine.

This paper contains a useful summary of all the many side effects of animal-derived trypsin and enzymatic treatments used to liquefy sputum – contrasted with the minimal side effects experienced with N-acetylcysteine. Interestingly there has been a renewal of interest in acetyl cysteine in the Millennium and the drug has been used both for respiratory (6.5% of USA patients with CF take inhaled acetyl cysteine) and gastrointestinal problems in CF (Lillibridge CB et al. Oral administration of n-acetyl cysteine in the prophylaxis of "meconium ileus equivalent" J Pediatr 1967; 71:887-9; Gracey M et al. Treatment of abdominal pain in cystic fibrosis by oral administration of n-acetyl cysteine. Arch Dis Child 1969; 44:404-405).

More recently the relation to glutathione, in particular, has featured in recent references as N-acetylcysteine is an effective precursor of cysteine for tissue glutathione synthesis. Apparently CFTR is responsible for glutathione transport and there may be intracellular accumulation of glutathione in cystic fibrosis (Childers M. Medical Hypotheses 2007; 68:101-102.)


One of many publications by Dr Robert Denton from Philadelphia. As the effect of chest clapping and vibrations was considered to be helpful in moving bronchial secretions, the effect of rapid repetitive percussion with a mechanical device was examined in 23 patients with CF who had moderate and marked pulmonary involvement.

The study with a mechanical percussor (figure 10) is complex and impressive, even involving a "control percussor" that did not vibrate. Over a 12 minute period, there was a significant increase in secretions produced with the percussor + vibrations compared to percussor with simulated vibrations and unassisted postural drainage; this was significant in 19 of the 23 patients although the vital capacity did not change significantly.

**Figure 10**: Percussor in use. From the paper with permission.
This was the first of a number of papers on mechanical percussion as an aid to chest physiotherapy. Some years later in the UK the “Salford percussor” (Maxwell & Redmond, 1979 below; Flowers et al, 1979 below) received a cool reception from the UK physiotherapists. However, the delivery of vibrations by a jacket or vest eventually became part of standard approved therapy in the USA thanks to the work of Warren Warwick (Warwick & Hansen, 1991 below). Again this more recent mechanical aid, “the Vest”, was slow to find favour with physiotherapists in the UK!

The first study of fatty acids in blood and tissue lipids of patients with CF. The fatty acid composition of chylomicrons and adipose tissue from children with CF who had variable degrees of fat malabsorption was compared with the values from controls. There was a relative decrease in linoleic acid and increased palmitoleic and oleic acids. Subsequently the abnormalities have been explained as related to liver disease, the basic defect and the intestinal malabsorption. <> Prof. Bob Elliott and colleagues from New Zealand published several papers showing improvement in the clinical state with supplements of medium chain triglycerides even to the extent of returning the sweat electrolytes to nearer normal values (Elliott RB. Aust Paediatr J 1972 below; 8:217; Elliott RB, Robinson PG. Arch Dis Child 1975; 50:75-78; Elliot RB. 1976; 57:474-479). However, subsequent studies failed to substantiate their findings (Davidson GP et al. Aust Paediatr J 1978; 14:80-82. [PubMed]; Chase et al. Pediatrics 1979; 59:428-432 below).

This is the first record of enlarged submandibular glands in CF – a feature which is sometimes quite marked (figure 11). During their studies on secretory activity of the salivary glands the authors noted many patients had enlarged submandibular glands. The submandibular glands of 300 normal children, 106 with CF and 20 with chronic pulmonary disease were examined. Enlarged submandibular glands were palpated in 92% of children with CF and only 2% of healthy controls and those with chronic pulmonary disorders. The presence of enlargement can be helpful when considering a diagnosis of CF.

A report from the Princess Margaret Hospital for Children, Perth, Australia. This is one of the early reports of “tetracycline teeth”, although the authors noted that Shwachman had described tooth discoulouration in 40 of 50 children who had long term treatment with tetracycline (Antibiotics Annual. New York. 1958:692). (also Zagaralli et al, 1960 above and 1963 below). The present authors noted pigmentation of infant’s teeth at a maternity hospital follow-up clinic; many of those affected had not been jaundiced – the usual explanation given for tooth discoulouration. The co-author Hilton had previously observed skeletal pigmentation with tetracycline, so the possibility of a relation to tetracycline administration was investigated. 50 out of 64 babies had received tetracycline in the newborn period and 46 had yellow or brown pigmentation of their teeth with or without enamel hypoplasia. The more tetracycline, the greater the change in tooth colour. Earlier Buyske et al had noted bone pigmentation by tetracycline and chlorotetacycline in animals (Buyske DA et al. J Pharmacol Exp Ther 1960; 130:150-156). [PubMed]

A commentary on the relatively recently described sweat test by Harry Shwachman and the article is full of good advice. While the sweat test is specific for CF Shwachman emphasised that the following factors were crucially important in diagnosis. Maintaining a high degree of suspicion noting the great variability of the disease; the presence of elevated electrolytes alone does not establish the diagnosis; many factors influence the result – not least the experience of the laboratory; diagnosis should not be made lightly but only after careful appraisal of the patient, the family history and laboratory evidence. Heterozygotes cannot be detected with the sweat test.

One suspects that over diagnosis was a relatively common problem in Shwachman’s experience due false high values of sweat electrolytes – this article discusses some of the confounding and other factors that affect the test. A key publication from Charlotte Anderson’s unit in the UK first documented the frequent overdiagnosis of the condition in the UK (Smalley et al, 1978 below) and was of great importance in alerting UK paediatricians to the problem.

A black infant admitted with bronchopneumonia at 8 months was diagnosed by three positive sweat tests as having cystic fibrosis. He died after 37 days. At autopsy, in addition to bronchopneumonia, the pancreas showed typical changes of cystic fibrosis. The authors note that at the Babies Hospital New York only 2 children of 397 cases were black infants an incidence of approximately 0.5% (di Sant’Agnese Am J Med 1956; 21:406).

At this time only 2% of people with CF were over 20 years of age. Two of the 4 adults studied died and were autopsied. In all the recognition of CF had been only after years of illness. Interestingly the use of hypertonic saline was mentioned as causing “symptomatic improvement” – eventually, some 40 years later, this was confirmed in a large trial (Elkins et al, 2006 below). Functional abnormalities were: airway obstruction, stiffening of the lungs, increased arterial carbon dioxide and reduced arterial oxygen saturation. The authors concluded the primary cause of the respiratory disease was obstruction of the airways secondary to impaired flow of abnormal bronchial mucus. They suggested that the practical conclusion would be to search for methods that could be used for mobilisation of the mucus from the airways. Subsequently such treatments as hypertonic saline or rhDNase (Pulmozyme) proved to be an effective means of improving and preserving lung function.


One of the early reports of colomycin, administered as an aerosol, achieving “satisfactory blood levels”. Reference is also made to Mensi E (1958) in this paper. Colomycin has had three phases of popularity in treating people with cystic fibrosis. Phase 1. As Gram negative infections, including Pseudomonas aeruginosa (Ps. pyocyanea as it was then), became more of a problem during the Sixties, intramuscular colomycin was the only effective injectable antibiotic. Robert Stern recalls how, in the early Sixties, he first started infusions of intravenous colomycin in Cleveland prompted by the extreme pain of the intramuscular injections in an emaciated girl with CF who already had an IV infusion running for hydration purposes. The IV route gradually replaced the painful IM route particularly when carbencillin became available in 1968. However, when gentamicin became available in 1968 this drug replaced colomycin as first line treatment for P. aeruginosa in people with cystic fibrosis. Phase 2. Interest revived in nebulised colomycin following the short report from Leeds (Littlewood et al, 1985 below) of the successful eradication of early colonisation with P. aeruginosa in CF using nebulised colomycin - an observation later confirmed in Copenhagen (Valerius et al, 1991, below) and a number of other small studies from Europe. According to Hoiby, nebulised colomycin was also introduced into the treatment of chronically infected patients in Copenhagen in 1987 on the strength of the initial report from Leeds. It is interesting that none of these early reports was accepted in the USA (even the excellent trial of Valerius et al, 1991 with its striking results) and it was some 15 years before early eradication of P. aeruginosa became widespread in the USA. Phase 3. As most resistant P. aeruginosa remained sensitive to colomycin, the intravenous use was again evaluated for strains of the organism which had become resistant to other antibiotics; it was found to be effective with an acceptable level of side effects (Conway et al, 1997 below) There was a detailed multi-author ten year review of Colomycin and its role in the treatment of CF published in 2000 (Littlewood JM et al. Respir Med 2000; 94:632-640 below)


There was considerable interest in possible abnormalities of the autonomic nervous system considered to be in some way related to the basic defect. The authors found significant differences in the pulpillary reactivity between people with CF and controls.

Holzel in Manchester had found normal levels of acetyl cholinesterase in various tissues and concluded any cholinergic over-stimulation was not due to absence of the hydrolysing enzyme (Holzel A et al. Lancet 1962; i: 822-823 above). Autonomic abnormalities were later confirmed by Davies et al, (N Eng J Med 1980; 302:1453-1456 below) and more recently were reviewed by Mirakhor A et al. (J R Soc Med 2003; 96 Suppl 43:11-17. below). Although there was considerable interest in autonomic abnormalities this knowledge does not appear to have made any contribution to either the treatment or the understanding of the basic defect. There was a later report of excessive finger wrinkling in people with CF when their fingers were immersed in warm water and this phenomenon has been related to autonomic function (Elliott, 1974 below).


The first report of optic neuritis in four children with CF on long term chloramphenicol – a complication which had been reported first in 1952 by Wallstein & Snyder (1952 above) in a woman with inflammatory bowel disease who after five months developed optic neuritis and peripheral neuritis. Later a number of reports in people with CF were reviewed by Harley RD et al (Trans Am Acad Ophthalmol Otol 1970; 74:1011-103). Numbness and tingling of the peripheries preceded the ocular signs which appeared to be related to the total dose received. It was suggested that 25 mg/kg/day for not more than 3 months was relatively safe. Fortunately, visual acuity usually recovered soon after stopping the drug but may recur if treatment was resumed. (Also Huang N et al. J Pediatr 1966; 68:32-44).


Patients with CF failed to show a significant decrease in their sweat electrolytes after administration of oral 9-alpha fluorohydrocortisone (3.0 mg per square meter for two days).
Parents, siblings of people with CF and controls all had a significant decrease in the concentration of their sweat electrolytes after this challenge – for example the fall in chloride in parents was -40.8%, in controls - 43.6%, in siblings -35.6%, but people with CF only had -1.1% reduction in their sweat chloride level.

This was a practically useful paper when there was a problem with diagnosis and there was a marginal sweat test result – particularly pre-1989 before genetic mutations could be determined. We used the test on a number of occasions and found it to be helpful when the diagnosis was in doubt and the sweat test result borderline with chloride values of around 50 – 70 meq/l. Margaret Hodson also found the fludrocortisone suppression test useful in adults with marginal sweat test results (Hodson ME et al. BMJ 1983; 286:1381-1383.) [PubMed]


An interesting paper by workers with extensive experience in rectal biopsy. The histological picture was characteristic of CF in many patients. When the histological picture of rectal "mucosis" is present it is specific for CF as shown here (figure 12) and it cannot be confused with any other rectal condition. It was not clear as to the proportion of cases of CF could be diagnosed with certainty – six of 11 patients with CF examined in this study showed definite diagnostic changes. Understandably, rectal biopsy never became popular as an additional diagnostic aid for CF; although ion transport abnormalities in the rectal mucosa were described in number of later studies (Veeze et al, Gatroenterology 1981; 101:398-403; Hardcastle et al, 1991 below).

Figure 12: CF rectal specimen on left and normal on right. With permission of the Lancet.


The incidence of chronic bronchitis in parents of people with CF (obligate heterozygotes) and controls was similar to that reported for the general population – which was remarkably high at that time being 17% of men aged 40-60 years and 8% in women. The authors concluded that “the heterozygous state for fibrocystic disease of the pancreas could not be implicated as an important cause of chronic chest disease or of peptic ulceration”. These results agreed with those of Anderson et al. Med J Aust 1962; 1:965. These results may not apply today as chronic bronchitis was remarkably common in the general population then due to atmospheric pollution and tobacco smoking.


Report of more than three years of daily chloramphenicol in patients with CF without toxic effects in 50 patients studied and in post mortem records of 23 others. Later one fatal case of aplastic anaemia was encountered.(also Denning et al, 1963 above; Huang et al. 1966).

1963 Rick W. Untersuchung zur exokrinen function des pancreas bei zysticher pancreas-fibroses. (Pancreatic exocrine function in CF of the pancreas). Medizinische Welt 1963; 42:2158-9. An early report of pancreatic function in CF showing reduced volume and reduced bicarbonate secretion. (Quoted by Wong LTK et al, Gut 1982; 23:744-750). Also pancreatic function was reported by Maddock et al, 1943 (above), Kopelman et al, 1985 (below) and Hadorn et al, 1968 (below). Hadorn’s work seemed to have had more impact (possibly as published in English) and is generally regarded as making the major contribution to pancreatic function testing in people with cystic fibrosis.


Viscosity measurements were determined on secretions obtained via tracheotomies from 2 patients with CF with the use of N-acetylcysteine aerosol which produced a greater fall in the viscosity of the secretions than did a control aerosol (also Webb 1962 above). The authors suggest that "The combination of this safe method of mucolysis with energetic postural drainage and physiotherapy

Obviously at the time there was considerable interest in this new mucolytic agent whose free sulphhydryl group reduced the disulphide linkages of mucoproteins. Subsequently it was the subject of a number of publications in liquefying sputum, improving abdominal pain and treating meconium ileus but never became popular in the UK as part of the pulmonary treatment. Although a subsequent review found no evidence of benefit (Duivesteijn YC & Brand PL. Acta Paediatr 1999; 88:38-41), Ratjen et al (Eur J Pediatr 1985; 144:374-378) found in a 12 week oral trial of NAC, ambroxal and placebo that "although no clinical differences could be observed between the three groups, significant impairment in the placebo group was found for trapped air and FEV1 when compared to the active groups, suggesting a therapeutic effect of ambroxal and NAC in CF". More recently the relation to glutathione has caused renewed interest in the drug which, when given orally in high doses, provides a source of glutathione and apparently reduces airway inflammation (Tiouvanziam R, et al. Proc Nat Acad Sc 2006; 103:4628-4633).


A short anecdotal report of long term use of oxacillin (an anti-Staphylococcal antibiotic available since 1962) in 15 patients with CF many of whom were receiving other antibiotics – mainly chloramphenicol. However, it did show that oxacillin was safe and that resistance on the part of S. aureus did not develop even after prolonged use although the organism was eliminated in only three patients – presumably because most had “advanced pulmonary involvement” and chronic entrenched infection by the time the treatment was started.

This is the first report of long term anti-Staphylococcal therapy, a treatment now recommended in the UK for all children with CF under three years of age although its prophylactic longterm use is still the subject of debate. Essential facts which have become apparent are that resistance to the antibiotic does not develop and the frequency of S. aureus positive cultures is reduced when patients are receiving long term anti-Staphylococcal therapy. The possibility of an increased likelihood of culturing P. aeruginosa becomes less relevant when a policy of early Pseudomonas eradication is routine the clinic – unfortunately this was not the case in North America until recently. Also less likely when a broad spectrum antibiotic is not used. However, In Leeds, where lifelong long term fluocoxacillin for most patients has been the policy since 1975 and early eradication of P. aeruginosa has been practiced since around 1984 – both the prevalence of chronic S. aureus infection of 14% is low (Southern et al, 1993. In: Clinical ecology of cystic fibrosis. Escobar H et al. (eds). Excerpta Medica Internat Congr Series 1034: 129-132) and chronic P. aeruginosa infection is well below average at 18.1% for the whole clinic and only 4.3% for those children less than 11 years of age (Lee et al, 2004, below).


Four infants with CF fed either human milk or soya milk had severe hypoproteinaemia. The onset of oedema was around two months. Death was usually between 8-16 weeks. Soya was definitely contraindicated in infants thought to have CF. Subsequent studies showed less nitrogen absorption from soya feed than from one based on evaporated milk (Fleisher et al. J Pediatr 1964; 64:349). A further instance was reported by Menton and Middleton in 1944 (above) and the first detailed report being that of Wissler & Zollinger in 1945 (above). Also Shahidi et al, 1961 (above). So soya based feeds definitely seem to be contraindicated for infants with cystic fibrosis.


One of the early papers discussing the peculiarities of this organism that was isolated with increasing frequency from people with CF, in particular the so-called "mucoid" form. Initially there was considerable discussion about the pathogenicity of P. aeruginosa in CF which initially was questioned by some clinicians. Pseudomonas aeruginosa, isolated from the respiratory tract of a group of patients diagnosed as having CF, attained the ability to produce in its capsule a material which was insoluble in certain organic solvents, such as ethanol. The capsule obtained from P. aeruginosa isolated from infected individuals who did not have CF was ethanol-soluble. This alcohol-insoluble mucoid from the CF P. aeruginosa could be demonstrated to persist after sequential subcultures of the organism. (also Doggett et al, 1966 below).


One of a number of papers on this subject which have appeared since that of Lloyd & Robitzek in 1952 (above) most of which showed surprisingly good results of lung surgery in people with cystic fibrosis. This report concerns surgery for severely affected segments of lungs of 21 patients with CF. Two became symptom free, 13 improved and 3 had poor results including cardiac arrest, eventually fatal collapse of the remaining lung and one had fatal multiple thoracic sepsis.

Sydney Gellis (1914-2002), the ever-sceptical editor of the Year Book of Pediatrics (Sydney Gellis, 1965-66 Year Book of Pediatrics), commented that there were obviously some who were not “afflicted by the contagion of enthusiasm exhibited by those who work closely with cystic
fibrosis...The discovery of the basic cause of the disorder and hopefully some form of substitution therapy must be the focus of the efforts in the disease. One could comment that it had it not been for the efforts of those "affected by the contagion of enthusiasm exhibited by those who work closely with cystic fibrosis" as Gellis put it, over the years, the impressive improvement in outlook would never have occurred! Also there was certainly a great need for such enthusiasts in the Sixties.


This book (figure 12.1) describes one of the first, if not the first, substantial CF meeting in the UK. Chaired by Professor Douglas Hubble of Birmingham, the contributors included most of those in the UK who had significant involvement with CF at the time including Drs Winifred Young, Archie Norman, Tony Jackson, John Batten, Cedric Carter, Lynne Reid and David Lawson. Dr Lloyd Rusby, of the Chest and Heart Association, noted that the Cystic Fibrosis Research Foundation was started in 1962 to raise funds for further research; also a group of parents based in Somerset "devote largely to the exchange of emotive and dismal family news". Sir Robert Johnson describes how attempts were made to absorb this Somerset Group in the Chest and Heart Association and to make that the main Cystic Fibrosis organisation in the UK but fortunately that failed as the charity would have been concerned with too wide a range of disabilities to give adequate emphasis to cystic fibrosis. However, these efforts gave rise to considerable concern until the Cystic Fibrosis Research Trust was formed (1964 details below).

Among the presentations at this meeting, Lynne Reid (scientist) implied that CF resulted in an abnormality of mucus which predisposed to infection and this abnormality could occur at an early stage but did not seem to be present at birth and "what is not so clear is why infection arises from impaction of uninfected mucus". "Perhaps the proportion of the different cell types is abnormal; from this, differences in the final constitution of the final secretion may follow".

Archie Norman (paediatrician) gives a detailed account of the clinical features ending - "To sum up cystic fibrosis should be remembered as a possibility in a newborn baby who takes his feeds well and yet fails to thrive, in an older baby who develops whooping cough and in the toddler with rectal prolapse. It should be considered in any older child with clubbing of the fingers or with a cough that never quite clears up".

John Emery (paediatric pathologist from Sheffield), discussing the laboratory aspects concluded - "I suggest that you do not send 24-hour specimens of stool to the laboratory for quantitative fat. A half minute scan of a drop of stool under the microscope will usually tell you much more". 20% trichloracetic acid is advised to test meconium for the increased protein in meconium ileus and the X-ray plate method for trypsic activity. After a review of the various tests available including the sweat test Emery wisely observes "Cystic fibrosis is by no means an 'all or none' disease and in my opinion should never be diagnosed or excluded on a single test".

Winifred Young ("research clinician") one of the leading CF paediatricians describes how their treatment at the Queen Elizabeth Hospital was intensified in 1955 due to their failure to arrest the incidence and progress of the pulmonary complications. Tony Jackson,(consultant paediatrician), reviews the improvement in outlook that occured following this change. Criteria for adequate antibiotic therapy were now considered to be -

1. Early treatment of the first lower respiratory infection with high doses of antibiotics by aerosol and other routes until clinical recovery and elimination of Staphylococcus Pyogenes judged by three negative swabs.
2. Continuous antibiotic prophylaxis for at least three months after lower respiratory infections.
4. Adequate treatment of all subsequent lower respiratory infections.

Considerable emphasis was placed on maintaining adequate nutrition and nearly half their patients were above the 25th centile for weight.

Dr David Lawson gave a thoughtful concluding talk on the future. As "there is as yet no wisp of smoke over the horizon of our knowledge" "we must deal with the problem as it is". This symposium gives an insight into the situation regarding CF as seen by the very few professionals in the UK who were familiar with the condition.

**1964 UK CYSTIC FIBROSIS RESEARCH TRUST IS FORMED**

The UK Cystic Fibrosis Research Trust was formed in 1964 on the initiative of the late Mr John Panchaud,(figure 13) whose daughter Caroline had cystic fibrosis.

The details surrounding the formation of the CF Trust were described in 1984 by Sir Robert Johnson, also a CF parent. He recalls that John Panchaud's father-in-law was a man called Percy Lovely, a man highly respected in the City of London and a Member of the Common Council. At this time the Chairman of the Dock Labour Board was Lord Crook who lived in Carshalton. In 1963 Lord Crook and the National Dock Labour Board gave a cocktail party at the Board's headquarters...
on the Albert Embankment in London to which Lord Crook invited a friend - a neighbor from Carshalton, Dr David Lawson. David Lawson was a paediatrician at Queen Mary’s Children’s Hospital in Carshalton and himself a CF parent. Among the other guests, at what was a City function for business dignitaries, were by chance, Mr. and Mrs. Lovely. In the course of the party, Dr Lawson espied Mrs Lovely. She was apparently a lady of some elegance wearing on this occasion a particularly edible hat! Having attracted or so it seems the attention of this young Dr Lawson and finding out that he was a doctor, she poured out her heart to him about the problem of her grand daughter Caroline. It was left that she would get her son-in-law, John Panchaud, to phone David Lawson to arrange a meeting.

So it was at that cocktail party, in the unlikely setting of the National Dock Labour Board headquarters in London, that one has the origin of the Cystic Fibrosis Research Trust. The consequence was that John Panchaud went to see Dr. Lawson and together they evolved a plan. David Lawson’s first suggestion was that they should set up a medical or scientific steering committee. John Panchaud proposed that this committee should include Dr Lawson and the physician who was looking after his daughter Caroline at Great Ormond Street Hospital - Dr Archie Norman. Eventually Dr Lawson became chairman of the steering committee which included Dr Archie Norman, Dr Cedric Carter, the geneticist from GOS, Dr Winifred Young (figure 8) of the Queen Elizabeth’s Children’s Hospital Hackney in London and Dr Lynne Reid a scientist working at the Brompton Hospital in London; they were soon joined by Dr John Batten another physician from the Brompton.

In July 1963, John Panchaud had his solicitor draw up the necessary legal documents for the formal creation of the charity. One of the first Trustees was Mr. Percy Lovely and as a result of his and John Panchaud’s contacts in the City they got together a Board of Trustees, including as originals Mr Joseph Levy and Lord Crook. others were Lord Bossom and there were other prominent figures in the City. The inaugural meeting of the new CF Research Trust was held on February 20th 1964 in the Mansion House in the City of London, under the auspices of the Lord Mayor, Sir James Harman.

John Panchaud, Joseph Levy and Percy Lovely were the prime movers in fundraising for research into something of which scarcely anyone had heard. Initially the individual trustees organised fund raising but soon the fund raising base need widening and the initiative was taken by Dr Archie Norman. He selected one of the mothers attending his clinic to organise the first group in London. There was increasing interest by parents in the groups and more formed around the UK.

Sir Robert Johnson says that he looks back on those days with great emotion for suddenly there was hope. Suddenly there was something one could do to fight back. A chance even to win. For those who were involved those days still mark a turning point in their lives. Much of the above detail has been taken from a lecture by Sir Robert Johnson, “History of Cystic Fibrosis Research Trust”, at the CF Trust’s 20th Anniversary Weekend at Brighton in June 1984.

Mr Joseph Levy CBE BEM (figure 14) was Chairman of the CF Research Trust for 20 years, from soon after its formation in 1964 until 1984 when his son, Mr Peter Levy OBE succeeded him, followed by Mr Duncan Bluck CBE until I (Jim Littlewood) became chairman in 2003. Many in the UK CF community, patients, parents and professionals, have reason to be grateful to Joe Levy, to Peter and the Levy family for their continuing and generous support in many areas.

The name of the organisation changed to the Cystic Fibrosis Trust in the mid Eighties at the request of the scientists on the Research & Medical Advisory Committee. They considered it was now not only a “research” Trust in view of the increasing proportion of the funds that were used for care of the increasing number of people with CF who were surviving and to support the many developing CF centres in the UK.

Ron Tucker OBE (figure 15) was appointed the first Director of the CF Research Trust in 1965 after many years of work with youth clubs in Lancashire and London. Apparently an interview panel was assembled to appoint a new Executive. Ron Tucker, who was a friend of Joe Levy, was on the panel. There were no suitable applicants and he was asked if he was interested - fortunately he was! Ron proved to be an inspirational central figure in the development of CF care and research in the UK. He was widely respected by patients, parents and professionals throughout the UK and abroad. He was very supportive of the many CF centres which were developing during the Eighties in the UK and very supportive of any paediatricians who showed the slightest interest in CF. He was instrumental in the appointment of both a CF research fellow (doctor) and a CF Nurse Specialist in Leeds when our unit was developing during the early Eighties and subsequently also supported many other developing provincial CF centres. He also encouraged many families with CF to come to Leeds for our Comprehensive Assessments when their local care was not available or he considered it to be unsatisfactory.

An early detailed report of the poor nutritional state and growth of 50 children with CF studied serially. The significant retardation of weight gain and growth particularly in adolescent and pre-adolescent children was severe with the medians for height and weight being only between the third and tenth centiles for age. Skeletal development was delayed in 38% of children. Not surprisingly there was a significant relation between the severity of the malnutrition and the pulmonary status. Better weight gain and growth occurred when the chest was treated – improvement being most marked in infants. Presumably a number of previously under-treated children were referred to this clinic and so the initial improvement was impressive. Unfortunately, many children deteriorated after a short period of improvement, succumbing to their advanced pulmonary disease which had been a major factor in the first place.


An early report of pulmonary hypertrophic osteoarthropathy in a girl of nine years (figure 16) with CF and severe pulmonary disease. Often asymptomatic in the early stages there is later aching and tenderness along the shafts of the long bones and around the joints. Shwachman commenting on this report said he had seen five or six instances in patients with severe pulmonary disease. Also he notes the condition is mentioned in Harris et al, Post Grad Med 1963; 34:251.

The degree of clubbing can be quantified in various ways. Sinniah D & Omar (Arch Dis Child 1979; 54:145-146) used a shadowgram technique which we later used in the Leeds clinic (Pitts Tucker et al, Arch Dis Child 1986; 61:576-579 below).


This is the second most frequent cause of chronic pancreatic disease in children. Six children are described with what became known as the Shwachman–Diamond Syndrome. It is one of a number of conditions eventually recognised as separate entities from cystic fibrosis. The authors advised that the condition should be considered in children at first suspected of having CF but who had repeatedly normal sweat electrolytes. In 1967 Burke and colleagues (Burke V et al. Arch Dis Child 1967; 42:147-157) reported 19 children with the condition from Royal Children’s Hospital Melbourne having published a preliminary report in 1965 (Colebatch JH et al Lancet 1965; ii: 496). Burke et al commented that in 1964 Bodian et al (Acta Paediatr Uppsala 1964; 53:282) from
Great Ormond Street, London had described two children with congenital hypoplasia of the exocrine pancreas both of whom had variable neutropenia and thrombocytopenia but which "did not receive special comment" – which is not entirely true. Bodian et al did however provide a useful review of a previous 18 histologically proven cases in the literature.

This was an important paper for paediatricians dealing with children who had CF as it identified a specific condition (exocrine pancreatic insufficiency, bone marrow dysfunction, skeletal abnormalities and short stature with normal sweat tests) likely to be encountered in specialist CF centres. In fact we identified five such children with the Shwachman-Diamond syndrome in Leeds over 20 years in the course of investigation of children considered initially to have cystic fibrosis.


Although an unusual protein content in the meconium of infants with meconium ileus had been described by a number of authors (Glazmann E, Berger H. Ann Paediat 1950; 175:33 above; Buchanan & Rapoport Pediatr 1952;9:304 above; Green M et al. Pediatr 1958; 21:635 above), the present study was to determine if meconium from infants with CF who did not have meconium ileus also had an abnormal protein content as perhaps this could be "used in a predictive manner" i.e. for neonatal CF screening.

In this study, using immunoelectrophoresis, the meconium from five infants with a family history of CF (1 – 5) was examined for increased protein. The three of these infants with CF (1,2, & 4) had obviously raised albumin levels which did not occur in the two unaffected infants (3 & 5) nor in two healthy control infants (6 & 7) (figure 17).

Figure 17: Electrophoresis of meconium in this study.

This study, from Salt Lake City, was the first to demonstrate increased albumin in the meconium of all CF infants and to suggest the finding could be used in a "predictive manner". Later Schutt & Isles (Arch Dis Child 1968; 43:178 below) from Bristol in the UK showed that the increased albumin could be recognised very simply by using the Albustix dipstick test designed for testing urine for albumin; this method eventually formed the basis of the BM Meconium test used with variable success in several neonatal CF screening studies during the Seventies (In Europe by Stephan U, et al. Pediatrics 1975; 55:35-38 below; in Wales by Ryley HC, et al. Arch Dis Child 1979; 54:92-97 below; in the UK by Evans et al, 1983 below).


Dr Doershuk (figure 18) recalls that Dr William Wallace, Chairman of Paediatrics at the Babies and Children's Hospital, Cleveland had been approached in 1957 by a parents' organisation - the "Cousins Club" - one of whom had already lost a child with CF and had another deteriorating from the condition. They asked Dr Wallace to start a "research orientated treatment programme for CF" which they offered to fund. To develop this programme Dr Wallace appointed a young paediatrician, Dr Leroy Matthews (figure 19) to plan and initiate the "comprehensive and prophylactic (preventive) treatment programme" for the treatment of cystic fibrosis. The programme which developed eventually became the model for the CF Foundation CF centres programme (also Doershuk et al, 1964 & 1965 below).

Figure 18: Dr Carl Doershuk. From Postgraduate Medicine 1966; 40:550-562

Three important areas of treatment were the obstructive pulmonary lesion, the secondary infections and the pancreatic deficiency and nutritional state. Treatment was early and comprehensive even started before symptoms - where this group differed from others and as such were ahead of their time. This paper describes the "comprehensive therapeutic regimen" which so influenced CF care in N America.

Veteran CF physician Dr Warren Warwick of Minnesota has "fond memories of two great stars – Harry Shwachman and Leroy Matthews". Of Leroy Matthews he writes - "Leroy Matthews, the greatest genius CF has seen, single handedly established the value of Comprehensive Treatment, laid the ground work for Pediatric Pulmonology, organised and led the CF Centres as well as planning and directing excellent research. He made only two mistakes. He allowed his "Comprehensive Treatment" plan to be equated with "mist tent therapy" so when the mist tent was discredited many also felt the Comprehensive Care Program was discredited. And he tried too hard to control his diabetes and suffered hypoglycaemic brain..."

A detailed evaluation of the results of the Cleveland comprehensive therapeutic regimen. 96 consecutive patients were followed for 18 to 60 months (average 37 months) and evaluated using a modified Shwachman score. 82% improved, 11% remained the same, and 4% showed progression beyond their initial status and only 3% died – none were less than five years of age. Patients who were regarded as having reversible pulmonary changes were reviewed separately in 1965 (Doershuk et al, Pediatrics 1965; 36:675 below).


Good results were reported in the group of children treated prophylactically with little progression over an average of 4.5 yrs. The early intervention and prophylactic approach was not the usual policy at this time and most clinicians waited until symptoms developed - even experts such as Paul di Sant’Agnese. In this study 98 consecutive patients had been followed for an average of 4.5 years and the clinical course of 49 were considered to be on prophylactic therapy was significantly different from the accepted natural course of the disease and from the 49 patients who had irreversible lung damage when first seen. No evidence of significant progression of the pulmonary state was seen in any of the prophylactic group. No deaths occurred in this group and the annual mortality rate was only 2% for the whole group. Their findings supported the need for early diagnosis and prophylactic treatment.

Sydney Gellis (always a sceptic regarding the treatment of CF!!) in the Year Book of Pediatrics questioned whether more mild cases had been included; also whether the improved survival could not have been due entirely to antibiotics and to none of the other methods of treatment described such as mist tents, aerosols, segmental postural drainage. di Sant’Agnese also observed that in one series of older patients (Shwachman et al, 1965) the diagnosis had not been made in many until teen age years suggesting they had a milder form of CF. Certainly patients with CF diagnosed later in childhood, who were included in some of the early adult series, undoubtedly more frequently would have had milder CF gene mutations as was confirmed in later studies (Gan K-H et al, 1995 below). Rather surprisingly di Sant’Agnese questioned the need to start the full prophylactic programme in all patients as soon as the diagnosis is made and agrees with most other clinicians that at that time that treatment is not started “until there is indication of incipient pulmonary involvement”. This view regarding the start of treatment is interesting and in these days of neonatal screening, failure to start early microbiological monitoring, early eradication treatment of respiratory pathogens and early nutritional intervention, would be regarded as unacceptable.


In the mid Sixties Sir John Batten (figure 20) started the first clinic in UK for adults with CF at the Royal Brompton Hospital, London. This clinic eventually became the world’s largest centre for adults with cystic fibrosis. In the UK it was the only large clinic for adults with CF until the Eighties as there were so few adults surviving. Sir John remained closely involved in the developments of CF care in the UK and with the work of the UK CF Trust eventually becoming its President from 1986 to 2003. He was physician to the Her Majesty the Queen from 1974 to 1989.

1965 The International Cystic Fibrosis (Mucoviscidosis) Association was formed.

In 1965 the International Cystic Fibrosis (Mucoviscidosis) Association (the predecessor of CF Worldwide) was formed in Paris under the medical chairmanship of Paul di Sant’Agnese. Guido Fanconi was appointed Hon. Chairman, George Barrie as lay President and Prof. Rossi Vice Chairman of the Medical/Scientific Council. The aims of the association were to improve the care of children and adults who had cystic fibrosis, to foster research and to disseminate information. This was the start of the International CF (ICFMA) now CF Worldwide meetings, which take place every 4 years.

1965 Kopito L, Mahmodian A, Townley RRW, Khaw KT, Shwachman H. Studies in cystic fibrosis: analysis of
UK CF clinics, such as this, were not more widely adopted throughout the UK. the attitudes of the general paediatricians, that the effective treatment regimens at the few large
It is a reflection of the much inferior medical communication systems in those times, or perhaps
trouble and who, at 5 years, were still considered to be free of bronchitis (Mearns, 1969).
and intensive physiotherapy – before 1957 they had 50 infants who, at a year, had no significant
the 1950s their young patients had received prophylactic erythromycin and nebulised neomycin
secondary effects of the basic defect at an early stage could significantly improve prognosis. From
meticulous clinical and microbiological follow-up and treatment reflecting their care in the Sixties
As early as 1972, Drs Margaret Mearns and Winifred Young published encouraging results of their
children with CF compared with in only 7% in 60
This was an important report as the presumption that an infant with meconium ileus definitely had
CF on one occasion to my knowledge resulted in an incorrect diagnosis of CF – a situation
overlooked for some 10 years. A child of 10 years who had been treated in the neonatal period for
meconium ileus was subsequently treated as having cystic fibrosis. In an outpatient clinic a
medical student asked the consultant paediatrician the result of the sweat test. It was eventually
discovered, after a search through the notes, that the child had never had a sweat test performed
doing the diagnosis. So a sweat test was performed which proved quite negative as did all
the other tests for cystic fibrosis. So the diagnosis was reversed. Subsequently the parents took
legal action against the paediatric consultant concerned.

1965 Mearns MB, Young W, Batten JC. Transient pulmonary infiltrations in cystic fibrosis
This was the first description of allergic bronchopulmonary aspergillosis (ABPA) occurring in two
children with cystic fibrosis. A subsequent study from this group showed precipitating antibody to
Aspergillus to be present in 31% of 122 children with CF compared with in only 7% in 60
Winifred Young (1909-1969) (figure 8) was appointed as a research clinician at the Queen
Elizabeth Hospital for Children Hackney Road London in 1943 and established a cystic fibrosis clinic
there in 1950. Winifred Young and Margaret Mearns (figure 21) were treating children with CF at
the Queen Elizabeth Hospital for Children, Hackney, London – at the time one of the few CF clinics
in the UK. Children who survived were referred from there (along with those from Archie Norman's
clinic at Great Ormond Street) to Dr John Batten's adult CF clinic at the Royal Brompton Hospital,
London.
As early as 1972, Drs Margaret Mearns and Winifred Young published encouraging results of their
meticulous clinical and microbiological follow-up and treatment reflecting their care in the Sixties
(Mearns, 1972 below). These were further indications that vigorous meticulous treatment of the
secondary effects of the basic defect at an early stage could significantly improve prognosis. From
the 1950s their young patients had received prophylactic erythromycin and nebulised neomycin
and intensive physiotherapy – before 1957 they had 50 infants who, at a year, had no significant
trouble and who, at 5 years, were still considered to be free of bronchitis (Mearns, 1969).
It is a reflection of the much inferior medical communication systems in those times, or perhaps
the attitudes of the general paediatricians, that the effective treatment regimens at the few large
UK CF clinics, such as this, were not more widely adopted throughout the UK.

Douglas Holsclaw (figure 22) who was a colleague of Harry Shwachman's, reviewed experience since 1944 of
109 infants with meconium ileus from the Hospital for Sick Children, Great Ormond Street, London. The
paediatric surgeons were Mr Herbert Eckstein and Mr Nixon. Half the infants with uncomplicated meconium ileus, 18% with a perforation and 24% with gangrene of a loop of bowel, survived. Of those treated surgically 41% survived after primary anastomosis, compared with 72% after a Bishop-Koop procedure (Bishop & Koop, 1957 above). Only 25% of those with a double barrelled ileostomy survived. Only 20 of 46 survivors reached one year and only seven lived over five years – virtually all died of pulmonary complications. However, there seemed to be a steady improvement occurring as nine of the 10 most recent cases survived.
Douglas Holsclaw published extensively over subsequent
in this series only 8 were diagnosed in the first year and only 34 of 65 were diagnosed less than 10 years. It is almost certain, as eventually shown by mutation analysis, that many of these late diagnosed patients had milder mutations.

Shwachman considered the most important single advance in treatment (as did others) was the introduction of broad spectrum antibiotics in 1948. The authors mention many aspects of management now regarded as features of optimal care.

“A few minor changes evolved over the years that may play a greater role than we are able to quantitate. Factors that have to deal with the economic, emotional and psychological problems of parents and of growing children having a disease expensive to treat and with an unpredictable future. Our constant availability for their guidance, the close and harmonious relationship to the family physician or paediatrician and of highly skilled experts in our medical centre, our attempt to secure financial assistance and to provide continuous long-term care by the same group of individuals regardless of the age of the patient, coupled with efforts to instruct our parents and above all our positive approach undoubtedly contributes to the relative success of our programme and survival of some of these patients beyond adolescence.”

These main components of good CF care have remained much the same over the years. One particular feature stressed by a number of the successful CF paediatricians over the years has been availability of the doctor for advice and continuity of care by the same group of individuals – two features which are less readily available in the modern UK National Health Service. However, one point must be made - many paediatricians in the USA - including Shwachman - were initially slow to refer their patients to chest physicians treating adults most of whom lacked the knowledge and experience to continue providing the expert treatment the patients had received to achieve their adult status. One factor may have been the problems with medical insurance arrangements.


An early description of fatty infiltration of the liver (steatosis), which can result in gross hepatomegaly and is, in part, reversible when the intestinal malabsorption is treated and the nutritional state improved. The child reported in this paper presented at two years five months with an enlarged liver which “extended to the pelvic brim” and marked generalised oedema – no manifestations of pulmonary disease were noted at the time.


These are useful non-invasive tests for confirming pancreatic insufficiency used for many years – chymotrypsin being preferred to trypsin as it is more stable. Their value was confirmed in subsequent reports (Brown et al, 1988 below). This present study used the method of Haverbach BJ, et al, (Gastroenterol 1963; 44:588-597). There was clear separation of CF and non-CF and the authors concluded it to be reliable in identifying those children with cystic fibrosis. Chymotrypsin values were : in CF < 58 ug/g and in non-CF > 75 ug/g stool and trypsin: in CF < 30 ug/g and in non-CF >80 ug/g stool.


There were visual changes in nine (27%) of 33 patients with CF who had received chloramphenicol in total doses of 81-283 g. The authors mention another patient treated with 135 g of chloramphenicol over 4.5 months (Cocke JG, et al. J Pediatr 1966; 68:27). The authors state that although visual disturbances had been described in children with CF and advanced respiratory disease (Bruce et al. Arch Ophth 1960; 63:391) only advanced respiratory changes were present as an explanation; however, these authors later described four children with eye changes due to chloramphenicol (Denning et al. J Pediatr 1963; 63:878) as did Huang et al. (3rd Interscience Conference Antimicrob Chemother 1963:79). Such patients with eye changes had always received prolonged treatment with chloramphenicol. The eye symptoms usually improved when the drug was stopped. Regular tests of vision were advised when the drug was used for prolonged periods.

In 1950 Dr Nancy Huang was appointed as research assistant at St Christopher’s Hospital for Children in Philadelphia where she became a faculty member and developed a major CF centre where she worked until her retirement in 1979.

Raised immunoglobulin levels were noted in many people with cystic fibrosis. Subsequently the raised levels were shown to relate to the severity of the lung involvement. The levels of serum immunoglobulins were very high in patients with advanced chest involvement. They are a very useful clinical marker of the severity of the chest infection. A later study showed that children with lower immunoglobulin levels had a better prognosis (Matthews WJ et al N Eng J Med 1980; 302:245-249).

The authors found abnormalities in response to darkness, stress and recovery from stress. They considered at the time these findings were possibly being related to the basic defect. Autonomic abnormalities were first suggested by Roberts in 1959 (above). Also Holzel et al, 1962 above; Rubin et al, 1963 above; Davies et al, NEJM 1980; 302:1453-1456 and more recently reviewed by Mirakhur A et al. (J R Soc Med 2003; 96 Suppl 43:11-17).

1966 Doggett RG, Harrison GM, Stillwell RN, Wallis ES. An atypical Pseudomonas aeruginosa associated with cystic fibrosis of the pancreas. J Pediatr 1966; 68:215-221. Another of the many papers published by Doggett on the atypical "mucoid" Pseudomonas aeruginosa isolated from 43 of 62 cultures from 78 children with CF. It was a highly mucoid variant of the organism which was insoluble in ethanol-benzene (figure 23) and was impossible to eradicate once established (also Doggett et al, 1964 above). The authors observe that "until such a means of control is found ... clinics that treat groups of CF children may find it good practice to separate those already having Pseudomonas from those not infected with the organism, especially those having inhalation therapy".

Doggett is usually credited with recognising the significance of the mucoid form of Pseudomonas in people with CF and the conversion from non-mucoid to mucoid after acquisition of the former but not in people who do not have cystic fibrosis. Also it is interesting that, even at this stage, he was suggesting that segregation of Pseudomonas-positive from Pseudomonas-negative patients would be good practice – some 35 years before such segregation was introduced into all CF centres in the UK – in a few with great reluctance on the part of the clinicians!

Figure 23: Legend below picture. From paper with permission.

Experience of Winifred Young from London - only one of 42 patients had ocular changes from chloramphenicol; 425 g having been given to this patient over 15 months. Various other findings were considered unrelated to drug therapy including four with squint, nine with tortuosity of the retinal vessels, one with blurring of disk margins – appearances considered due to more severe lung disease. Eighteen children had various short course of chloramphenicol with no obvious ill-effects.

First of a number of publications on survival in the UK from Dr. Archie Norman’s unit at Great Ormond Street, London. Life tables for 1943-1964 showed that 80% died by 5 years and 90% by 10 years. Infants with meconium ileus, 25% died by 1 week and 75% by 3 months.

Sydney Gellis, in an editorial comment in the corresponding Year Book of Pediatrics, observed that “Despite claims to the contrary, cystic fibrosis of the pancreas continues to carry a gloomy prognosis. Present day therapy is helpful but offers relatively little, and a realistic alteration of the course of the disease will require a major breakthrough in discovering the aetiology”. Gellis,
although a distinguished paediatrician was not an expert on CF and in this prediction was obviously quite wrong for the outlook improved steadily over the years long before the aetiology was identified during the Eighties.

The authors did not find previous reports of pneumothorax in the American literature – only in text books. However, prior to this report there had been sporadic reports of pneumothorax in CF in the literature from 1947 (Fanconi G, Metaxas-Buhler M. Helv Paediat Acta 1947; 2:289-295). Also Doershuk (1964) had one example in 96 patients.

This present report is of sudden onset of left pneumothorax in a 12 year old girl with CF whose chest showed “far advanced changes” at the age of 7.5 years (figure 24). With a tube and drainage the lung expanded in 2 days (figure 25); she was discharged in 6 days but died 4 months later from her pulmonary disease.

Pneumothorax is a complication which occurs in those with more advanced chest damage and is now very rare in children with CF. For example in the 2004 UK CF Registry there were no children reported as having pneumothorax and only one in an adult with cystic fibrosis.

A detailed evaluation of 11 patients aged five to 17 years. Not unexpectedly extremely marked intrapsychic and interpersonal conflicts occurred in all cases. The authors considered that both children and parents required psychological treatment also the doctor-family relationships required further study.

The editor of the Year Book of Pediatrics, Sydney Gellis, felt the almost unbearable psychologic problems should be treated actively. He questioned “the support conferred by the CF Foundation which undoubtedly makes the family more knowledgeable about the condition and more capable of coping with the problems involved, but also makes parents more aware of the prognosis”. He suspected that a minister or priest would prove more helpful than a psychiatrist in assisting parents.

It was just this approach, exemplified by Gellis, that made the situation even more unbearable for the parents who usually appreciated an aggressive therapeutic approach, as adopted by paediatricians such as Shwachman, di Sant’Agnese and Leroy Matthews even if they realised that the end was inevitable. It was at the CF centres of such paediatricians that this approach resulted in a steady improvement in prognosis over the years so that median survival had increased to over 38 years by 2009 without any specific treatment to correct the basic defect being available. So obviously Gellis (1914-2002) disliked psychiatrists as well as paediatricians who treated children with cystic fibrosis!! It is perhaps not surprising that not one of his 206 publications listed on Medline concerned cystic fibrosis. He was described as “the quintessential pediatric generalist who was not deterred by the growing army of “-ologists”! Certainly"generalists" who failed to appreciate the advantages of specialization were a hindrance in the attempts to improve the outlook for many people with CF.

Robert Denton describes the in vitro mucolytic activity, the clinical response and the effect of oxygen and nebulisation on the stability of a 20% solution of N-acetylcysteine. In vitro dispersion is more complete than with saline. There was an improvement in drainage from the upper respiratory tract but failure to improve drainage from the lower respiratory tract. Nebulisation did not alter the chemical structure. The present method of mask administration may not affect the lower respiratory tract (also Webb 1962 above; Reas 1963 above)

It is interesting that N-acetylcysteine is so rarely used for people with CF in the UK when some of the earlier published work is so impressive with regard to its mucolytic effect. More recently the relation to glutathione has caused renewed interest in the drug which when given orally in high

Figure 24: Massive left sided pneumothorax.  Figure 25: Air resolved in 2 days with tube and drainage.


Experience from Dr Winifred Young’s unit in London where 36.5% of 63 children with CF had discoloured teeth due to tetracycline treatment (also above Shwachman H, et al, Antibiot Ann 1958-59; 692 above; Zegarelli et al, Pediatr 1960; 26:1050 above; Wallman IS, Hilton HB. Lancet 1962; i: 827 above)


Winifred Young and Tony Jackson were paediatricians at the Queen Elizabeth Hospital Hackney where there was one of the few CF clinics in the UK which was started by Winifred Young in 1950. Margaret Mears joined the staff there soon after. Further data from these authors is described above in Cystic Fibrosis. A symposium. Report of a meeting on 28th May 1964 at the Wellcome Foundation London. Chest and Heart Association.


This paper from Cleveland, from one of the most respected clinical groups in the USA, was considered to provide evidence of the efficacy of mist tent treatment which was by this time widely used in the USA. After three control periods the addition of mist tent therapy to an otherwise comprehensive treatment programme resulted, over the next two months, in significant decrease in functional residual capacity, residual volume and ratio of residual volume to total lung capacity - changes that were maintained over the next year.

In commenting favourably on this paper at the time Paul di Sant'Agnese implied that clinicians with experience of treating people with CF would agree with the authors’ findings and stated – “the results reported here confirm the clinical observation of the value of mist tent therapy...it is generally accepted by almost all clinicians, who have had adequate experience with this disease, that most patients have considerable benefit from such a treatment programme”. Di Sant'Agnese continued “we must conclude from all available clinical, physiologic and pathologic evidence that, in addition to the judicious use of antibiotic agents, all types of inhalation and physical therapy should be used in therapy of pulmonary involvement of cystic fibrosis”. Despite this support from leading CF clinicians of the time, the treatment was later discredited and gradually abandoned by most of them in the early Seventies (See also Doershuk et al, 1968 below). Mist tent therapy was never popular in the UK. But perhaps the possible benefits of nocturnal humidification will be re-examined in the light of the low salt theory of pathogenesis of the respiratory problems?


In the same issue of Pediatrics as Matthews et al, 1967 (above) paper on mist tent therapy, Mary Ellen Avery (figure 26) wrote a detailed critical review of mist therapy and concluded - "At present the technical advances in the generation of mists and knowledge of the deposition of particles exceeds knowledge of the role of mists in the treatment of respiratory disorders. Some evidence exists that viscous secretions can be thinned by mist; upper airway cooling and drying can be decreased by added humidity. So the doubts about mist therapy were beginning to be expressed. Mary Ellen Avery was Professor of Pediatrics at Harvard and the first woman-in-chief at the Children’s Hospital, Boston.


In 2001 Warren Warwick commented “After 10 years of grants funding the US CF Patient Registry and indirectly supporting the Canadian CF Patient Registry and the beginning of the International Registry, the CF Foundation decided the Registry should become the property of the CF Foundation. When the CF Foundation took over the operation they discovered what a bargain the $10,000 annual grant was. So after spending over $100,000 and still not finishing the analysis, they decided to give up the analysis as too expensive. They were shamed into doing the analysis when the Canadian Foundation provided funds and manpower to complete the analysis. The fallout was that the Canadian Foundation went its own way and beginning the International Registry was abandoned. All the data from the first 10 years of the US Registry, including the magnetic tapes, were transferred to the CF Foundation where they were somehow lost!”

This paper is included as it is one of the few reports from the UK of a survey between 1952 and 1962 from the North of England by Yorkshire paediatricians Richard Pugh of Hull and Douglas Pickup of Pontefract on behalf of the Leeds Regional Paediatric Club. During this decade 132 infants were confirmed as having CF among total of 546,764 births over 13 years – an incidence of 1/4142. Fifty six infants (42%) died in the first year. These findings would be typical of the situation in the UK at the time where virtually all children with CF were treated at local hospitals and there were no specialised CF clinics in most towns and cities – or even in most provincial teaching hospitals. So few patients survived childhood. A significant number of affected infants must have gone unrecognised in this study for the incidence in this part of the UK was later shown to be at least 1/2500 births.


A sodium sensitive electrode was used to measure parotid saliva sodium and showed a reasonable separation between CF (12-52 meq/l – 27.2 meq/l mean) and controls (3-15 meq/l mean 5.9 meq/l) with 4% in overlap values of 12-15 meq/l.

Unfortunately a later paper on CF screening showed “an undesirably wide” scatter of results in neonates which narrowed by 6 weeks (Lawson et al, Arch Dis Child 1967; 42:689). The method was never used for neonatal screening as not only was it unsatisfactory but also neonatal screening was not recommended at the time in view of the relatively ineffective treatment available in most of the UK. This situation still existed in the Eighties at the time of the West Midlands and Wales trial of neonatal screening (Chatfield et al, 1991 below). Unfortunately the considerable amount of work on salivary electrolytes never had a significant clinical application (Chernick et al, 1961 above; Chernick & Barbero, 1963 above).


This is a concise account of present treatment recommendations by the American Thoracic Society Committee on Therapy. However, Dr LeRoy Matthews appears to be the only CF expert on the committee - in fact the only person on the committee to have published any papers on CF according to a search of Medline! Treatment by nebulisation is one of the most effective measures where particles of liquid are deposited in the airways and is recommend three or four times a day. Also mist tent therapy is recommended “to add large amounts of water to the pulmonary secretion to liquefy them and thus promote their removal” for “all patients throughout life” and “studies have demonstrated that mist therapy is one of the most effective measures available”. There is a blunt statement that “prophylactic antibiotic therapy is of no value”. The contents are presumably influenced by the views of Leroy Matthews and as such represent a comprehensive account of current treatment with a section on Comprehensive Care. At that time Matthews was a leading supporter of mist tent therapy (Matthews et al, 1967 above).


A detailed paper dealing with many practical aspects of the sweat test. Burns and blisters at the site of the electrodes were shown to be caused by penetration of acid generated electrolytically to the vicinity of the patient’s skin. Prevention of these and other errors are discussed in detail. In particular, the rapid evaporation which can occur from the collection pad resulting in up to a twofold increase in concentration of the sweat in 30 seconds – probably this is the major cause of over diagnosis from false high results.

For some years after the Fifties sweat tests were performed in many small laboratories on an occasional basis and many mistakes were made – these were usually false positives and were due to evaporation leading to false high sweat electrolyte values (Smalley et al, 1978 below).


Reported blockage of the cystic duct by white mucous material. Previous reports on the gall bladder by Jones et al, 1958 (above) and Esterly & Oppenheimer, 1962 (above).


A detailed report of autopsy findings of 84 patients with CF. There was widespread dilatation of respiratory bronchioles and alveolar ducts in 29 but significant parenchymal destruction in only three patients. John Esterly and Ella Oppenheimer of Johns Hopkins Baltimore made numerous contributions to the knowledge of the pathology of cystic fibrosis.


The first reports of respiratory function tests in children with CF had been performed by West et al, 1954 (above). In Margaret Mearns's study from London the results of respiratory function tests were correlated with clinical and radiological findings. Thirty three of 85 patients had normal FEV1 and FVC but the day to day variability were considered to limit the value of the respiratory function tests. Reversibility in response to bronchodilators was described. Twenty eight had minimal X-ray change, stable and normal; 16 with localised damage had greater reduction in FEV1 than FVC; extensive damage was associated with significant reductions in both. The tests were a valuable aid to clinical assessment especially in those patients with no or little radiological
changes. Margaret Mearns observed that “the present study shows that without the mist tent (given such prominence by Leroy Matthews and others in the USA during the Sixties), but using intensive treatment for acute respiratory illness and very close follow up from the time of diagnosis, children presenting without permanent lung damage can remain well and maintain good respiratory function over a period of years”.

These were early days for respiratory function tests in many paediatric clinics in the UK. The Vitalograph was the first widely available bellows spirometer for non-specialist use. But most general paediatricians in the UK did not have a Vitalograph although most eventually used the Wright peak flow meter. Also few children treated in general paediatric clinics lived to an age when the results would have been reliable – say over six years.

The first report of night blindness in CF due to vitamin A deficiency in 16 year old girl who had been seriously under-treated and who had major social problems. Later reports showed abnormal nocturnal vision due to vitamin A deficiency (Rayner et al, 1989 below) but not where vitamin levels had been monitored regularly and maintained in the normal range (Ansari et al, 1999 below).

This is the first report that men with CF were infertile. Repeated sperm analyses in 8 male patients with CF always showed aspermatia with low volume and increased turbidity. All the men were in reasonable general condition. In nine patients at autopsy and in nine biopsy specimen the testes showed active spermatogenesis but half the sperms had malformed heads. Various explanations for the infertility were discussed including malnutrition, vitamin deficiencies and genetic causes – but not at this stage were abnormalities of the vas deferens suggested as a cause. Although “transport difficulties” of the sperms due to viscid secretions in the male are mentioned there is no mention of the maldevelopment of the vas deferens which was eventually found to be the main reason for the infertility; this was described first by Kaplan et al, in 1968 (below) and also by Valman and France in 1969 (below).

Histological abnormalities of the testis and structural abnormalities of the vas deferens are described; this is the first correct explanation of the male infertility. Twenty five patients aged 17 to 31 years all had aspermatia. They could not identify the vas deferens in necropsy specimens from patients aged 5 to 20 years nor in 6 patients during repair of inguinal hernias. These findings provided an explanation for the previously reported infertility of men with CF (Denning et al, 1968 above). The vas deferens was represented by a thin fibrous cord or could not be located; the body of the epididymis was small or absent and the seminal vesicles were either absent, fused or represented in a dilated or bifid sac. The authors considered these were development changes rather than the result of duct obstruction as occurred in the pancreas (See Denning et al, 1968 above; Valman HB, France NE. 1969 below). Later a survey of US CF centres suggested that some 2-3% of men with CF may be fertile (Taussig LM et al. N Eng J Med 1972; 287:586-589).

Elvin Kaplan later recalled - “My year as a fellow with him (Harry Shwachman) was rich in clinical and personal growth. Harry expected each fellow to write a paper and he eventually suggested the topic he wanted me to explore. It was his idea, his insight and his direction that lead this paper and personal growth. Harry expected each fellow to write a paper and he eventually suggested the topic he wanted me to explore. It was his idea, his insight and his direction that lead this paper and personal growth. Harry expected each fellow to write a paper and he eventually suggested the topic he wanted me to explore. It was his idea, his insight and his direction that lead this paper and personal growth. Harry expected each fellow to write a paper and he eventually suggested the topic he wanted me to explore. It was his idea, his insight and his direction that lead this paper and personal growth.” (Fanos JH. Am J Med Genet 2008; Part A164A:284-293).

Warren Warwick has pioneered databases in CF and was responsible for starting the CF Foundation Patient Registry. He maintains that US paediatricians initially agreed to cooperate with his first CF database as they did not believe Leroy Matthews excellent results and thought the data may confirm their suspicion! (also Warwick & Manson, 1967).

One of a number of papers by Hadorn et al on stimulated pancreatic function in CF using a triple lumen tube. The method was used in a few CF Centres, including our own in Leeds, during the Seventies, but it was a difficult test to perform and very invasive for the children. The findings in the present group of 10 children with CF were a low volume of fluid and low bicarbonate output even when the enzyme concentrations were not markedly reduced. After intravenous injection of pancreozymin (P) bile stained juice high in enzymes is secreted. After secretin (S) injection the volume and bicarbonate concentration is increased but the enzyme concentrations are reduced. In CF the secretion of both is markedly reduced (figure 27). Also from the same group Zoppi et al. (Helvet Paediatr Acta 1968; 6:577-590) found a higher protein content in the pancreatic juice of both CF and non-CF pancreatic insufficiency using


Thirteen of 176 children with CF in the Melbourne clinic had normal fat excretion. Ten of these pancreatic sufficient patients (PS) had pancreozymin-secretin tests confirming that the water and bicarbonate secretion from the pancreas was more severely affected than the enzyme secretion. They secreted small volumes of pancreatic juice with very low bicarbonate content and but abnormally high enzyme concentrations. Evidence was presented that the pathological features in the pancreas could result from a failure to produce an adequate amount of electrolyte containing fluid. In the text they make the following important comments “it is possible that this (the extensive changes in the pancreas) is at least partially caused by the “organic fraction” which is abnormally concentrated in enzymes. Although proteolytic enzymes are originally present in an inactive form in pancreatic juice it is not unlikely that they may become activated if the flow of secretion is markedly reduced or stagnates. Furthermore, because the secretion is more concentrated and more viscous, blockage of tubules followed by dilatation of the acini may lead to their rupture, and the intraluminal material containing activated enzymes could spread into the surrounding tissue causing irritation and destruction followed by atrophy and fibrosis of parts of the pancreas or entire organ”

This is very likely to be the correct explanation for the early onset of the pancreatic damage starting with the electrolyte/fluid abnormality, now (but not then) known to be related to abnormalities of fluid and electrolyte transport across the cell membranes and analogous to the changes occurring in other organs – but earlier and more severe as the other organs do not have to contend with the damaging effects of the pancreatic enzymes. Of course, the abnormality of membrane transport had not been described at this stage.

Pancreatic function had been studied by Correia JP & Barros F. (Study of the exocrine function of the pancreas with secretin and pancreozymin. Journal do Medico 1963; 52:581-92). Rick (1963, above) produced an early report of pancreatic function in CF showing reduced volume and reduced bicarbonate secretion (quoted by Wong LTK et al, Gut 1982; 23:744-750). Also pancreatic function in CF had been reported first by Maddock et al, 1943 (above), and subsequently by Kopleman et al, 1985 (below). Hadorn’s work seemed to have had more impact (possibly as published in English) and is generally regarded as making the first major contribution to pancreatic function testing in CF.


Mist tents were still a very popular form of treatment in the USA in the late Sixties particularly in the Cleveland clinic. Ultrasonic nebulisers were said to be better then jet nebulisers for mist tent therapy. However, towards the end of the decade the use of mist tents was increasingly questioned until eventually a number of studies failed to show benefit from the overnight treatment (Bau et al, 1971 below; Norman & Hall Practitioner, 1971; 206: 786-789 below; Motoyama et al, Pediatrics 1972; 50:299; Chang et al, Am Rev Resp Dis 1973; 107:672 below). Certainly the Mistogen compressor nebuliser system gave a very fine dense mist into the tent.


An early suggestion for neonatal CF screening from detection of the increased protein in meconium, a finding which was first described by Buchanan & Rapoport, 1952 (above). Wiser &
Beier, 1964 (above) had described raised albumin in the meconium of infants who did not have meconium ileus. Meconium from 49 infants with CF who were siblings of 196 people known to have CF were tested and only 4 gave a negative protein reaction (trichloracetic acid ring test and a slide agglutination test); 1600 control meconium specimens were all negative. The test was suggested as screening test for CF with 90% reliability. The authors stated “It is strongly recommended that mass surveys be undertaken only with accompanying facilities for the clinical investigation and treatment of the patients found”. This was very sound advice and lack of centre care for infants with CF detected eventually proved to be a main reason that a large UK Wales & West Midlands neonatal screening study in the Eighties failed to show benefit for the screened infants (Chatfield et al. 1991).

These were the first two children with CF in the American Indian population. Both patients had convincingly high sweat tests and clinical features and were three years eight months and one year 11 months when reported. A sibling of case one who died had the typical pancreatic changes of cystic fibrosis. Caucasian ancestry, if present, was very distant and only on one side of the family and then three generations back. It was suggested that the rarity of CF in Mongolian and American Indians may be related to their common Asian ancestry before the American Indians crossed the Bering Straits into the Western Hemisphere. [PubMed]

1968 The Danish CF Centre started at Rigshospitalet in Copenhagen.
Erhard Winge Flensborg (figure 28) diagnosed the first person with CF in Denmark in 1944. Soon after the Second World War he visited Dorothy Andersen in New York to discuss the Danish cases. Subsequently five patients were published by him in 1948 (Of the so-called congenital cystic fibrosis of the pancreas. Nord Med 1948; 39:1574). After a number of paediatric appointments he became head of the Paediatric Department TG, Rigshospitalet, Copenhagen where, in the mid-Sixties, he started the first Scandinavian CF Centre and founded the National Danish Cystic Fibrosis Association. The CF Centre in Copenhagen is today one of the leading international centres of CF research and clinical care. Flensborg retired in 1982 at the age of 69 years and had his 95th birthday in 2007 (figure 29).

Figure 28: Professor Flensborg in 1980 two years before his retirement. With permission of the Danish Cystic Fibrosis Association

A really memorable little cameo presentation by Dr Werner Schutt of Bristol at the UK Paediatric Research Society. The authors state “we have found a simple side room technique helpful in detecting the presence or absence of albumin in significant quantities in meconium”. Protein in meconium of 9 infants with meconium ileus was high at 70% compared with 9% in controls infants and 22% in other cases of neonatal obstruction (figure 30). The authors proposed, for the first time, a simple test using the Albustix, a urine dipstick test that turned blue in the presence of the albumin, to detect the increased albumin in the CF meconium. A solution of a few drops of water and a little CF meconium was mixed on a white tile, and the Albustix was laid on the tile with the tip in the solution. There was an impressive blue coloration
provided by Danish Cystic Fibrosis Association.

Figure 30: Protein electrophoretic strips from a) amniotic fluid, b) normal meconium, c) meconium from meconium ileus, d) normal serum. Reproduced with permission of the BMJ Publishing Group

intravenously.


Jean Feigelson told me this was the first instance of proven fertility in a man with cystic fibrosis. Shwachman reviewed the details with Feigelson and agreed with the diagnosis – hence Shwachman was included as an author. It is usually stated that 2-3% of men with CF are fertile and this is more likely with particular genotypes such as 3849-10kb C->T mutation (Dryfus DH et al. Am J Resp Crit Care Med 1996; 153:858-860).

1969 First meeting of European Working Group for Cystic Fibrosis - Interlaken
The meeting was suggested by Prof. Ettore Rossi of Berne (1915-1999) (figure 31) to discuss recent advances in cystic fibrosis research. So in 1969, the European Working Group for Cystic Fibrosis (EWGCF) was formed to provide an annual forum where people from the various disciplines, but with a common interest in CF, could meet and discuss their latest findings. Since 1970, there has been an annual meeting (except every four years when there is a meeting of the International Cystic Fibrosis Congress) in a different European country and organised in conjunction with the local CF association.

Professor Rossi was Chairman of the Department of Paediatrics of the University of Berne, Switzerland from 1956 until he retired in 1985. He was one of the central figures involved in the development of many areas of paediatrics in Europe, including cystic fibrosis. I met Professor Rossi only briefly on a few occasions - one incident left me with a lasting impression of his kindness and humanity. At an International CF Conference in 1980, when he was chairing a plenary session, he had no hesitation in informing one very senior presenter, who had just described of a study involving children with CF in numerous annual needle biopsies of the liver, in no uncertain terms, precisely what he thought of the ethics of the study! He was obviously held in high regard by those who knew him and described as an enthusiastic teacher, a serious hard working paediatrician and a superb medical friend - “the beloved father of hundreds of paediatricians in the whole world”.

PROFESSOR NIELS HOIBY HAS KINDLY GIVEN

Positive skin test reactions to common allergens were present in 50% of 37 patients with cystic fibrosis. Many subsequent papers reported an increase in atopy in people with CF although clinical manifestations of allergy have not proved a major problem with the exception of allergic bronchopulmonary aspergillosis and more recently allergic reactions to intravenous antibiotics – which are now both major problems. (also Price et al, 1979 below).


One of the early studies on glucose metabolism from Great Ormond Street, London by Tony Milner at a time when few patients survived to an age when they developed diabetes. However, it had been predicted that this might occur as patients became older. Glucose and insulin levels were measured after oral glucose and intravenous glucose, glucagon and tolbutamide in 61 children with CF. The results suggested that the increased incidence of impaired glucose tolerance was due to a defect in the release of a glucagon-like substance from the alimentary system in addition to defective islet cell function. (also Rosan et al, 1962 above; Huhnstock K & Schwarz G, 1961 above).


David Lawson was one of the first paediatricians to suggest long term anti-Staphylococcal prophylactic chemotherapy. Eventually this treatment was supported by a controlled trial in CF screened infants in East Anglia, UK (Weaver et al, 1994 below). Prophylactic flucloxacinil is now recommended for all CF infants in the first 3 years by the UK CF Trust's Expert Antibiotic Group (2002 and 2009) although the findings are not accepted in North America.

I was impressed by David Lawson's approach and from 1975 all CF children for whom I was responsible were on long term cloxacillin and later flucloxacinil from soon after birth, if screened, or from the time of diagnosis. The results of this policy were reported in 1993 by Kevin Southern at the Madrid ECFS meeting. Of 110 patients attending our unit for all their care at that time only 16 (14.5%) had chronic *Staph. aureus* infection – individual group prevalence in 0-4 years nil, 5-9 yrs 14.7%, 10-15 yrs 22%; furthermore some of those patients had been referred to our clinic already chronically infected with *S. aureus*. The Leeds CF centres still have most patients on continuous flucloxacinil and there is a very low prevalence of chronic Staphylococcal infection. It is also interesting that despite the publications suggesting anti-Staphylococcal prophylaxis leads to a higher prevalence of *Pseudomonas* infection, this does not occur if there is also a policy of regular cultures and early *Pseudomonas* eradication.

David Lawson, whose daughter had CF, was one of the founders of the UK CF Research Trust in 1964. He maintained that earlier diagnosis, by improved neonatal screening, was essential for improvement of results as by the time the diagnosis was presently made lung damage was already present.


One of the early reports of the abnormalities of the vas deferens which explained the infertility first reported in detail by Carolyn Denning et al - first at the CF Club 1966 and later published in 1968 (above). Also this paper confirmed the abnormalities of the vasa deferentia described by Kaplan et al, 1968 (above) as the cause of the infertility and showed the changes could be variable. In Bernard Valman's study the post mortem appearance of the vasa deferentia in 10 boys with CF were reported. In all the vasa were either absent or reduced to a fibrous or muscular band suggesting that the mesonephric duct had been obliterated during the 10th or 12th week of fetal life (figure 32).


An early (possibly the first?) study of respiratory function in CF infants (figure 33). Total gas volume, dynamic compliance and mean pulmonary resistance were measured in 18 infants less than 9 months old. Nine infants with no infection and others with infections all returned to normal when treated with intermittent inhalations of propylene glycol 10%, glycerine 2%, in 0.9% saline 2ml + 0.25 ml of 2% orciprenaline 1-4 x daily.

More recent studies of infant respiratory function show a mild but consistent degree of airways obstruction and hyperinflation even in uninfected young infants with cystic fibrosis (Ranganathan SC et al, Lancet 2001; 358:1964-1965).

Opinions of many of the leading authorities of the time were divided but all agreed there was a need for clinical trials. The Europeans and North Americans were in favour of mist tents but UK were not. The discussion seemed to move towards nebulised antibiotics; Leroy Matthews was enthusiastic about nebulised gentamicin later used with carbenicillin by Margaret Hodson (Hodson et al, 1981 below).

The first convincing description of both coeliac disease and CF in a marasmic infant (figure 34) from David Burman’s paediatric unit in Bristol. The sweat test was re-checked when the infant was thriving and was strongly positive. In addition to the abnormal jejunal biopsy, which showed subtotal villus atrophy, the infant reacted violently when challenged with gluten at the age of a year. Subsequently children with both conditions were reported also by Goodchild MC, et al. Arch Dis Child 1973; 48:684-691; Katz A et al, Pediatrics 1976; 57:715). Later studies have shown a slight increase in incidence of coeliac disease in people with cystic fibrosis (Valetta EA, Mastella G. Acta Paediatr Scand 1989; 78:784-785 below).

A major milestone in the treatment of meconium ileus, the first being the surgical management described by Hiatt & Wilson in 1953 (above); then the Bishop Koop ileostomy (1957 above). This is the first reported use of diatrizoate maglumine (Gastrografin) enemas for meconium ileus. Later reported from Liverpool as effective in meconium ileus equivalent in older patients when given by mouth (O’Halloran et al, 1986 below).

For patients with troublesome abdominal pain, 5 ml of a 20% solution N-acetyl cysteine with 50% water was given four times daily. Five of the six patients ceased having pain within a week – the other patient refused to take the treatment. The authors were prompted to try the treatment by the first report of a 26 year old man with CF reported by Lillibridge CB et al,(J Pediatr 1967; 71:887) whose abdominal pain responded impressively with N-acetylcysteine 30 ml three times daily by mouth. A particularly useful report as the results of surgery for meconium ileus equivalent were still poor.

A review of the increasing doubts regarding the use of mist tent therapy noting that most of the liquid was deposited in the upper respiratory tract - although breathing through a wide bore tube was more effective. Although Leroy Matthews is mentioned as producing evidence of a beneficial effect (Matthews et al, 1967 above) it was suggested that trial should be given to all sorts of inhalation therapy for the individual patient, either intermittent aerosols or mist tents. A controlled trial seemed to be indicated.

Twenty eight severely affected patients were treated in the 5 years up to 1968 with the anabolic steroid norethandrolone. All the patients showed immediate improvement in appetite, activity and weight gain; also their respiratory function improved. Six patients died and there were a variety of side effects side effects including virilisation (also Kunstadter et al,
1961 above). However, there was great interest in this treatment as all else had failed to achieve weight gain in some of these patients. The subject was reviewed in 1981 by Richard Dooley (Anabolic steroids. In 1000 years of Cystic Fibrosis. Warren Warwick (ed). University of Minnesota, 1981).

A report of the use of intravenous gentamicin in a variety of respiratory infections including 30 patients with cystic fibrosis. Intravenous gentamicin was administered over periods ranging from three weeks to 16 months and the response to treatment was classified as good in 20 patients, moderately improved in 7 and ineffective in 3. The drug was reported as often valuable in infections due to Pseudomonas aeruginosa.