forbidden clones of cells arising in the lymphoid tissue of the pharyngeal region. Here the homeostatic mechanism is assumed to be broken down by the changed local conditions associated with streptococcal infection and re-established with the waning of the local infection. This is as yet no more than a working hypothesis which may stimulate experimental work toward the characterization of forbidden clones—if they exist.

Conclusion

This discussion of the auto-immune disease represents a purely theoretical study, but I believe it is important that we should have a clear theoretical background if we are to devise means to prevent or treat these conditions. One of the greatest difficulties in their study is our inability to produce analogous conditions in experimental animals. Where experimental models are not available there is perhaps greater justification for the speculative type of approach that I have used.

What I should specially like to leave with you is a sense of the existence of cellular populations within the body which, like a population of bacteria in a test-tube or rabbits in a continent, are subject to mutation, proliferation, death, and selective survival. The population dynamics of the body cells represents, I believe, the most fertile of all the broad fields of medicine that still await adequate study. Just as I completed writing these lectures, I found a new paper by Szilard (1959) putting into mathematical form a thought that has been becoming more and more insistent in my own mind—that ageing is essentially the integration of mutational damage to somatic cells. If this is true, and if I am correct in the interpretation of the pathology of immunity, and if the somatic mutational approach to cancer withstands the challenge of the virologists as I believe it will, then somatic mutation as an aetiological consideration may come to dominate the whole of medicine in so far as it is concerned with the waning half of human life.

The approach is an unpopular one—mutations are irreversible and there is no presently conceivable way in which the process can be prevented. Curative approaches, too, must be indirect and largely empirical. Medical science, however, is growing up, and I think it is time that we stopped fostering the naive expectation of the public that genetic anomalies, including feeble-mindedness, cancer, the degenerative disabilities of age, and death itself, will all eventually be overcome as surely as we can deal with pneumococcal pneumonia or malaria. There will always be much that we can do as doctors, but we must base our expectations upon facts and leave a belief in miracles to others.

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KARTAGENER'S SYNDROME WITH FIBROCYSTIC DISEASE

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Situs inversus has been recognized from antiquity; among the ancients Aristotle is said to have noticed two cases of transposed organs in animals. The Renaissance and its aftermath saw a renewed interest in anatomy; Fabricius, one of the successors of Vesalius at Padua and among whose pupils was William Harvey, described a case of reversed liver and spleen in the human in 1660; and Petrius Servius, in 1615, recorded a case of transplantation of the viscera (Lineback, 1920; Sherk, 1922). It was not until the early nineteenth century that the condition was first diagnosed clinically. By the latter part of the century such a diagnosis could be confirmed with accuracy by the newly discovered roentgen rays. Over 1,000 cases of this abnormality have now been recorded, and it has been estimated that it occurs as often as one case in approximately 1,400 of the general population (Johnson, 1949). It is not incompatible with normal health, however, and it is often related how Elisha Bartlett, a distinguished physician of his day, lived a normal life-span with complete transposition of the viscera. The condition itself may be complete or partial, when it may be limited to the abdominal or thoracic organs alone. It is often associated with numerous other congenital abnormalities (see review by Wood and Blalock, 1940).

Kartagener (1933) described a group of patients with bronchiectasis who had situs inversus, recognized in the main by the discovery of dextrocardia; his cases also had abnormalities of the paranasal sinuses. It has become general experience that the incidence of bronchiectasis and sinusitis in patients with rotational abnormalities is greater than that noticed in the general population; for instance, Adams and Churchill (1937) found that 21.7% of a series of patients with situs inversus studied by them had bronchiectasis; the comparable incidence of bronchiectasis in the general hospital population was 0.36%. In view of the association of bronchiectasis with the obvious congenital abnormalities in the situs inversus cases, the hypothesis has been advanced that this is one type of true congenital bronchiectasis, with cystic changes in the lung as a result of dissociated tissue held to be primitive foregut tissue occurring within the lung bud. It is the opinion of others, however, that the bronchiectasis is acquired from infected sinuses which are congenitally malformed. It is our purpose to record a further case of this syndrome in a patient in whom it seemed likely that the bronchiectasis and other clinical failures were associated with fibrocystic disease of the pancreas.

Case History

A man aged 20 woke on the morning of March 19, 1957, with epigastric pain. This at first came in spasms and was

likened to acute hunger. He took his breakfast and went to work complaining of a diffuse, intermittent, colicky pain, only to return home some hours later owing to a constant aching pain in the central abdomen. He felt anorexic and nauseated but did not vomit. Later in the evening the pain was felt more severely in the left iliac fossa, where it persisted until the time of operation. He had no frequency of micturition or dysuria. His bowels had moved normally earlier in the day.

On admission his temperature was 99.4° F. (37.4° C.) and his pulse rate 86. His tongue was moist but covered with a white fur, and there was marked halitosis. He was very tender in the left iliac fossa, with accompanying hyperaesthesia, and there was guarding and rebound tenderness at this site. He was noticed to have marked finger-clubbing. Chest examination revealed dullness and moist rales at the right base; the apex was palpated in the fifth right interspace 3½ in. (9 cm.) from the midsternal line, and liver dullness was present on the left side. A diagnosis of acute appendicitis with transposition of the viscera was made and appendicectomy carried out via a left iliac fossa incision. The caecum was withdrawn from the wound and the appendix was found to be tense and distended with pus at its tip, which was greenish blue in colour for ¼ in. (2 cm.). It was removed in routine fashion: abnormal rotation, the absence of the pelvic colon, and the presence of the liver on the left side of the abdomen were confirmed.

His past medical history was ascertained in detail. He was a first child of birth weight 8½ lb. (3,885 g.), whose parents were healthy; his mother's age at the time of his birth was 28 years. There was no history of chest disease in the family. He was breast-fed. From the age of 3 weeks until adolescence he was frequently in hospital because of recurring upper respiratory infections. At the age of 3 months he had a collapse of his right lung. As a child he was very susceptible to infections and failed to thrive properly. At 11½ years he was only 66% of his expected weight. At this time bronchiectasis at the left base was discovered. At 14 years a lipiodol bronchogram showed bronchiectasis of left middle and lower lobes. An x-ray film of his sinuses showed them to be small and underdeveloped. After this, though the possibility of surgical treatment for bronchiectasis was suggested, he did not report for further treatment until the onset of his acute appendicitis.

Special examinations were performed as follows.

Chest Screening and Bronchogram

X-ray examination of the chest showed dextrocardia and a left-sided aorta (Fig. 1); the left dome of the diaphragm was higher than the right probably owing to a left-sided liver. The gastric air bubble was present on the right side. Screening confirmed these changes, and a barium swallow revealed an indentation of the right side of the oesophagus opposite the aortic impression. The indentation was due to extrinsic pressure, probably an anomalous vessel, or possibly a double aortic arch. Bronchograms showed a bronchiectasis of the left lower lobe and lingula; only the proximal parts of the lower lobe and lingula filled, and these were obviously abnormal. Some homogeneous opacities previously noted at screening and thought to be cysts were outlined with contrast medium and shown to be dilated bronchi. The frontal sinus was underdeveloped and there was mucosal thickening in both maxillary antra. Electrocardiographic recordings showed changes typical of dextrocardia.

Investigations Relative to Mucoviscidosis

Chronic pulmonary disease in childhood or adolescence, if associated with failure to develop normally, should be investigated for the possible association with generalized fibrocystic disease or mucoviscidosis.

If pancreatic insufficiency is present the ratio of split to unsplit fat in the stool and its nitrogen content will vary from normal values, and this should indicate the lack of

the appropriate enzyme, lipase or trypsin. The daily fat excretion on a mixed diet was 8.7 g. (above 5 g. is evidence of steatorrhoea). Examination of the split and unsplit fat in the stool showed that 29% was split and 71% unsplit (normally as much as 80% should be hydrolysed to fatty acids). The nitrogen present in the stool was 3.94 g./24 hours. (Wollaeger *et al.* (1947) gave 0.8–2.5 g./24 hours as the normal range.)

Darling *et al.* (1953) showed that the sweat-gland secretion in fibrocystic disease was abnormally high. In this instance the trunk of the patient was heated and sweat was obtained from the neck region, which was perspiring freely. A rapid means of detecting the sodium chloride abnormality is to employ the test plates of Shwachman and Gahm (1956), in which silver nitrate and potassium chromate are embedded in an agar medium. In patients

FIG. 1.—Radiograph of chest showing dextrocardia. Note gastric air bubbles on right side and slight elevation of left dome of diaphragm. Lipiodol has been given into the left bronchial tree.

with abnormally high sweat-salt content, contact of the body with the surface of the plate produces a white precipitate. Consequently the method of digital imprint is used (Fig. 2).

Analysis of the electrolyte composition of sweat from the patient showed abnormally high values for sodium chloride within the accepted range for fibrocystic disease recorded by di Sant' Agnese (1956) (see Table). Analysis of salivary electrolytes showed the same trend: sodium 20 mEq, chloride 27 mEq (as sodium chloride) per litre (normal values: sodium 8.7–23.9 mEq/l., chloride 8.4–17.7 mEq/l.).

Values (mg./l.) for NaCl in Sweat and Urine, Showing Normal Range and Range of Determinations for Patient. The Values Quoted for Sweat NaCl (di Sant' Agnese) for Fibrocystic Disease—Sweat Chloride 50–160 mEq/l. and Sodium 80–90 mEq/l.

	Sweat from Mid-abdomen		Urine 24-hour Sample		Aldosterone Excretion in Urine (μg./day)
	Chloride mEq/l.	Sodium mEq/l.	Chloride mg.	Sodium mg.	
Normal	8–52	15–60	4,000–7,000	2,500–4,500	0.6–2
Patient	135–150	155–165	1,000–1,500	500–900	2–3

A 24-hour sample of urine, on a salt intake of 5–10 g./day, gave a mean reading of 2.039 g. of sodium chloride per litre (normal range, see Table). In view of the abnormal losses of sodium chloride in the sweat it seemed possible that reduction of sodium chloride in the average daily output of urine was due to active retention of sodium chloride to prevent excessive loss. Aldosterone excretion was determined to ascertain if excess of this hormone was being secreted to help effect this compensation. The excretion amounts were raised in two determinations above the normal range (Neher and Wettstein, 1955) (see Table).

The high sweat-chloride content was confirmed by the Shwachman test when a +++ reaction was obtained

(Fig. 2). This test was applied to the patient's parents and siblings. Both parents were negative, but one of the siblings showed a reaction equal in degree to that of the patient—without having any evidence of chest disease.

Miscellaneous

Examination of the oral mucosa for the presence of sex chromatin in the nuclei showed a complete absence of the destructive chromatin mass. The presumptive chromosome constitution is therefore XY. This examination was performed because of a possible link with other genetic upsets.

The blood group was O, rhesus positive, with genotype Rr (CDE/CDE).

The blood picture showed: haemoglobin, 74%; reticulocytes, 1%; P.C.V., 39%; M.C.V., 70 cubic microns; M.C.H.C., 28%, with an appearance typical of iron deficiency.

Agammaglobulinaemia was excluded by a normal plasma electrophoresis pattern. This examination was performed because of a possible association with recurrent chest disease.

Discussion

Many of the cases of situs inversus recorded in the literature, remaining undiagnosed till treatment by operation, were cases of partial transposition, which is known to occur in three main forms: there may be partial transposition of both the thoracic and abdominal organs, and transposition affecting the abdominal organs alone or the dextrocardia alone. Recognition of total transposition of the viscera in this instance enabled a diagnosis to be made and treatment to be planned as though the patient were the mirror image of a more normal individual. The presence of the apex beat on the right side, liver dullness transposed to the left side, where commonly gastric resonance is found on examination, and the shadow of gas in the fundus of

the stomach on the right side of the abdomen were the main criteria. Left-handedness is not present in higher incidence in patients with situs inversus, and this is an unreliable guide (Cockayne, 1937), but in cases where the diagnosis is in doubt as a result of discrepancies in the above findings a more reliable sign is the lower position of the right testicle (Cholst, 1947).

The anatomical abnormalities in situs inversus may be summarized as follows. The heart lies to the right of the midline, and its chambers are reversed, the apex being the right ventricle, from which rises the aorta. The aorta arches toward the right, giving off the innominate artery (which subsequently divides into the left common carotid artery and the subclavian artery), the right common carotid artery, and the right subclavian artery. The great veins empty into the left atrium, whence the blood passes into the left ventricle, the pulmonary arteries, the pulmonary capillary bed, the pulmonary veins, and the right atrium respectively. The thoracic duct lies to the right and empties into the right subclavian vein near its junction with the internal jugular vein. The lungs are structurally reversed, the right being bilobed and the left trilobed. Intra-abdominally, the cardia lies to the right of the midline and the lesser curvature extends toward the left. The spleen is on the right, and the gall bladder and liver (with reversal of the normal lobular arrangement of the latter) on the left. The entire intestinal tract is reversed, with the caecum and appendix on the left and the sigmoid flexure of the colon in the right iliac fossa.

The topography of abdominal pain is of interest when the alimentary tract of patients with malrotation is affected by disease. Cases such as this one tend to confirm the arguments for true visceral pain (see Brown, 1942), since the patients can be interpreted as experiencing the central abdominal pain merely as the artificial displacement of tissue from the midline. No matter how the gut has rotated or migrated to a new abdominal site, its nerve supply and sensory experiences remain that of a simple straight tube situated in the middle of the abdomen. The later sharp and more accurately localized pain of appendicitis is the result of irritation by exudate of the parietal peritoneum which has a cortico-spinal nerve supply. Although many cases of situs inversus are recorded in the literature, comparatively few in the experience of Hershman (1952) have been described with appendicitis: on the contrary, Blegen (1949) recorded 96 examples of appendicitis with transposition of the viscera, and in a proportion of his cases the pain was on the right side, although the appendix was on the left side.

The causation of situs inversus has been the subject of much doubt. In general, it has been regarded as genetically inherited, and the support for this theory has come largely from the study of the families in which this condition has been known to occur; alternatively, it has been alleged to result from some environmental upset of the fertilized ovum. Our patient was thought to have mucoviscidosis, since he had bronchiectasis, sinus infection, and anomalies of the sweat secretion and the exocrine secretion of the pancreas, consistent with this diagnosis (for review see di Sant' Agnese, 1956). Mucoviscidosis is a disease in which hereditary transmission by a recessive genetic mechanism is likely; the most acceptable hypothesis at the present time is that the disease is due to a gene or genes which cause overt disease in homozygotes and which give partial or no expression of the disorder in heterozygotes

FIG. 2.—Shwachman test on silver-nitrate-impregnated agar plate. Upper plate is normal control. Lower plate shows imprint of finger from patient.

(Childs, 1955). Whether this genetic inheritance is sufficient to provoke any inherited situs inversus as a genetic factor, or might influence the fertilized ovum as an acquired factor acting through its early environment, is a matter for speculation only. In support of the acquired theory of situs inversus is the fact that two environmentally acquired conditions—namely, agammaglobulinaemia and toxoplasmosis—have already been described in association with situs inversus (Collins and Dudley, 1955; Van Creveld *et al.*, 1948).

Since many cases of mucoviscidosis can have the latent type of disease and may pass unrecognized in the community except by the sweat-composition defect, it is possible that association between situs inversus and mucoviscidosis is more common than one at first imagines, and it might be the case that the Kartagener syndrome is a form of situs inversus associated with fibrocystic disease. The abnormality in the lungs and recurrent infection of the sinuses formerly led to the spontaneous belief that the lesions were almost certainly congenital in type, for the good reason that they occurred in the presence of such a pronounced congenital defect as situs inversus. If our case is not an exceptional one, an alternative view is now put forward—that the bronchiectasis and sinus infection may be occasionally associated with mucoviscidosis, and that, if searched for, concomitant defect such as faulty exocrine secretion of the pancreas and sweat will be found. It is supportive evidence for this theory that the defects in sweat composition were found in another member of the patient's family. Cases have been described in the literature which are capable of interpretation according to our hypothesis; for instance, Bergstrom *et al.* (1950) record two cases of the Kartagener triad, with two additional cases of bronchiectasis among six siblings. It is fairly well known that bronchiectasis arising in several members of the same family should arouse the suspicion that they have inherited some of the features of mucoviscidosis, and that examination of the sweat composition will usually not only confirm this but reveal other members of the family affected as latent cases.

Summary

A case of situs inversus viscerum is described requiring appendicectomy for acute obstructive appendicitis.

This patient with situs inversus also had had repeated attacks of pulmonary infection related to bronchiectasis and sinusitis, the syndrome described by Kartagener in 1933.

The patient had anomalies attributable to mucoviscidosis or fibrocystic disease—namely, abnormalities in sweat-gland secretion and in the content of the fat and nitrogen in the stool. He was aged 20 years—unusual in patients suffering from known mucoviscidosis. The anomaly of the salt content of the sweat was found in a sibling.

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PHYSIQUE AND HAZARDOUS OCCUPATIONS

A COMPARISON OF THE PHYSIQUE OF 160 ROYAL MARINES

BY

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The physique and choice of occupation of three groups of men serving in the Royal Marines have been studied. The initial object was to compare the physique of a particular branch known as swimmer-canoeists with that of branches not engaged in such severe training, but comparison of other trades also showed differences of interest.

1. *Swimmer-Canoeists* receive special training in canoeing in rivers and tidal waters, and underwater swimming for such purposes as underwater demolition and beach reconnaissance. Training is arduous and is unlikely to be survived by those who are not mentally and physically robust. Training is largely carried out at night. Underwater swimming in these conditions is a sufficiently trying experience in itself; it is the more so when it forms only one item amongst overland night marches, parachute drops, and heavy physical labour and exposure involved in canoeing. The group here presented represents the entire training staff of an establishment where swimmer-canoeists are trained; no trainees are included.

2. *General Duty Marines*.—This group consisted of a cruiser detachment of Royal Marines to whom I had access. As such they were engaged in the normal peacetime training of the Royal Marines, not so severe or exacting as that undertaken by group 1, but more arduous than that of many occupations. All were questioned about their intentions regarding volunteering in the future for more arduous training. Any having such intentions were excluded.

3. *Other Special Branches*.—A third group of men belonging to miscellaneous trades, not involving major hazard, were also studied. They comprised clerks, drivers, vehicle mechanics, and cooks. All those available to me at one given time were measured, with the exception of those relegated to their particular trade for medical reasons.

These three occupational groups might be expected to embrace gradually diminishing degrees of "somatotonia," the component of temperament described by Sheldon as correlating most closely with mesomorphy or muscularity. Somatotonia includes