impossible to forecast susceptibility and to anticipate respirator dermatitis. In this way the simple procedure of assessing susceptibility in newly joined men was denied, and prophylaxis was confined to early diagnosis—i.e., observation of the initial and evanescent symptoms, and early patch-testing. The most effective prophylactic measure, entailing much labour, time, and untold difficulties, besides problems of rubber supply, is naturally the recall of all potentially harmful masks and their replacement by innocuous varieties.

Prompt treatment in the earliest stages ensured a rapid cure, while the replacement of the respirator by one of an innocuous variety prevented the recurrence of this condition. Patients presenting themselves in the later stages yielded to treatment in from two to three weeks.

The early stage of erythema with mild irritation responded to dusting with calamine powder or talc, no other treatment being necessary. A more pronounced erythema with considerable irritation necessitated calamine lotion or Burow's solution (a 2½% liq. aluminium acetate).

The outstanding application of value in the later stages of vesiculation, weeping, and crusting was calamine liniment. Lotions, pastes, and creams made up in simple form or with varied ingredients proved of doubtful value and sometimes harmful. Phenobarbitone, gr. 1 to 2, helped to control the intense irritation and the resulting insomnia. In superadded pyogenic infection a 20% sulphonamide paste proved useful in clearing up sepsis. The early submental oedema required no special treatment, but with the onset of induration compresses of cataplasma kaolini proved effective in controlling its extension and in promoting resolution. The case which developed a fluctuant area in the submental induration and showed cutaneous and subcutaneous oedema in the cervical region responded favourably to aspiration. The dry scaly stage proved the most resistant one, but responded to boric ointment cautiously followed by an ointment consisting of salicylic acid gr. 10, ammoniated mercury gr. 10, and paraffin. flav. molle to one ounce. The conjunctivitis was treated by bathing the eyes with a 2% boric lotion.

A review of the treatment shows that while no royal road to success has been discovered, attention to detail combined with appropriate choice of mild ingredients in a suitable base ensures the best results.

Summary

Respirator dermatitis—a form of rubber dermatitis—was observed in 16 patients.

Two organic substances belonging to a group of compounds known as "accelerators" and "anti-oxidants," and used in the vulcanizing of rubber masks, were found responsible for the skin changes.

The dermatitis was classed as one occurring in predisposed subjects, who at first tolerate the irritants, but later develop a sensitivity to them—in short, a sensitization dermatitis.

The points in favour of this classification are discussed.

Aetiology, symptoms, signs, complications, and treatment are described.

Photographs showing the normal and pathological appearance of patients are included.

Gratitude is expressed to Surg. Capt. G. V. Hobbs, R.N., for his encouragement of this investigation; to Surg. Cmdr. A. Fairley, R.N., and his colleagues for the preparation of the experimental rubber disks and technical information about respirator manufacture; and to Mr. A. Hornbrook for the photography of patients.

P. Levine and others (*Amer. J. Obstet. Gynec.*, 1941, 42, 925) point out that erythroblastosis foetalis had been believed to result from antigen-antibody reaction on a purely theoretical basis before the part played in this condition by the Rh factor had been determined. The Rh factor in the foetal blood is transmitted as a dominant Mendelian gene from the father. Anti-Rh agglutinins have been demonstrated in the mother's blood, and the continuous action of these on the Rh-positive foetal blood over a period varying from weeks to months causes a progressive haemolysis of foetal blood. It is clear, then, that the immunizing substance can pass from the foetus to the mother through the placental barrier. As the Rh factor is probably limited to red blood corpuscles only, it is assumed that foetal blood in one form or another penetrates the villus in large enough quantity to immunize the mother.

TWO CASES OF REGIONAL ILEITIS (CROHN'S DISEASE)

BY

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Although scattered descriptions of this disorder are to be found in the medical literature previous to 1932, its clear recognition as a clinical entity dates from the publication of a paper by Crohn, Ginzburg, and Oppenheimer (1932). This paper was based on a series of 14 cases seen at the Mount Sinai Hospital, New York, and the disease has acquired the eponym "Crohn's disease." An extract from the original description will help to define the entity with which we are dealing:

"The disease is clinically featured by symptoms that resemble those of ulcerative colitis—namely, fever, diarrhoea, and emaciation—leading eventually to an obstruction of the small intestine, the constant occurrence of a mass in the right iliac fossa usually requiring surgical intervention (resection). The terminal ileum is alone involved. The process begins abruptly at, and involves, the ileo-caecal valve in its maximal intensity, tapering off gradually as it ascends the ileum orally for from 8 to 12 inches. The familiar fistulas lead usually to segments of the colon forming small tracts communicating with the lumen of the large intestine; occasionally the abdominal wall anteriorly is the site of one or more of these fistulous tracts.

"The aetiology of the process is unknown; it belongs to none of the categories of recognized granulomatous or accepted inflammatory groups. The course is relatively benign, all the patients who survive operation being alive and well."

Since 1932 it has become recognized that a similar non-specific inflammation may involve segments of the stomach, jejunum, ileum, and colon. The two cases described in this paper present some aspects of diagnosis and treatment.

Case I

The patient, an unmarried woman aged 22, was admitted to the Willesden General Hospital on July 14, 1941, having been diagnosed at another hospital as a probable case of Addison's disease. The onset of the illness was in Dec., 1940, the presenting feature then being diarrhoea. Some weeks later abdominal pain and vomiting were added. The pain first occurred in the epigastrium some 10 to 20 minutes after eating, but later in the illness it was more generalized, being felt all over the abdomen. Vomiting of bile or food slightly relieved the pain, which in any case disappeared after some 15 minutes. The pain was of a colicky character and often very severe. Diarrhoea was intermittent and would alternate with periods of constipation, which, however, did not obviate the pain. The patient became progressively weaker during the first half of 1941, and her weight fell from 9 st. 8 lb. to 6 st. 3 lb. The blood pressure was 95/60, and this, combined with some pigmentation over the abdomen and chest, suggested the diagnosis of Addison's disease, which appeared to be confirmed by chemical investigations carried out in May, 1941. Thus the serum sodium was said to be 270 mg. per 100 c.cm. (normal 320 mg.) and the chloride 545 mg. per 100 c.cm. (normal 560 to 620 mg.); the serum potassium was considerably raised, but it was recognized that the result was obviated by laking of the blood. In hospital (July 14, 1941) the serum sodium and chloride were found to be normal—330 mg. and 580 mg.; the fasting blood sugar low—65 mg. per 100 c.cm.; and the blood urea raised—60 mg. per 100 c.cm., the last-named probably associated with the existing dehydration. There were no special signs on physical examination, except some tenderness in the right iliac fossa. The temperature ranged between 98° and 102° F.; the pulse rate was about 96. Clinically the diagnosis of Addison's disease seemed improbable, and the therapeutic test of the daily injection of 20 mg. of desoxycorticosterone for 14 days was tried without any special improvement. (It is interesting that this high dosage did not produce oedema, as it might do in Addison's disease.) The sedimentation rate was raised—61 mm. in 2 hours—and a hypochromic microcytic anaemia was present: Hb 60%; erythrocytes 3,500,000 (average diameter

6.6 μ ; C.I., 0.7; leucocytes, 10,000 per c.mm.—polymorphonuclears 75%, eosinophils 4%, basophils 1%, lymphocytes 13%, and monocytes 7%. Examination of the stools revealed no pus cells or acid-fast bacilli; culture gave plentiful colonies of *B. coli* and a profuse growth of a non-haemolytic *Streptococcus faecalis*. Urine showed numerous oxalate crystals, but no other abnormalities and no acid-fast bacilli. The Mantoux test was positive, 1 in 1,000 dilution.

Radiological Investigation.—No evidence of any pulmonary lesion; no opaque gall-stones; no abdominal calcified glands; no calcification of suprarenal glands; no gastric lesion noted; appreciable pylorospasm and duodenal irritability and tenderness; barium enema: "The first evacuation studies are somewhat suggestive of a superficial colitis in the distal half of the colon."

The diagnosis appeared to be uncertain, but colitis and abdominal tuberculosis were thought of. This patient was seen by one of us (F. W. M. P.) on Aug. 7, when it was obvious that her condition was deteriorating. At that time she was having attacks of abdominal colic, although the abdomen was not distended. There was persistent slight tenderness in the right abdomen. It was considered that *tabes mesenterica* was the most probable source of her symptoms, and it was decided to conduct an exploratory laparotomy. The operation was performed on Aug. 19, under gas, oxygen, and ether, the abdomen being opened by a right paramedian incision. A typical condition of regional ileitis (Crohn's disease) in the acute stage was discovered. The terminal 15 inches of the ileum was swollen, red, and congested, but as yet quite free from adhesions to surrounding structures. As the patient's condition was not very good it was decided to limit operative intervention to a lateral anastomosis; consequently by this means a portion of healthy ileum was united to the transverse colon, but the terminal ileum was not excluded. The progress after operation was uneventful and the patient's condition showed considerable improvement. Her weight increased and the abdominal pains diminished in severity to a great extent, although they were not actually abolished. The sedimentation rate on Sept. 9 was still high—i.e., 1st hour, 42 mm.; 2nd hour, 47 mm.

The patient was allowed to leave the hospital on Sept. 16 for a short convalescence, and was readmitted on Oct. 6; by then her general condition had improved, but she had developed an ischio-rectal abscess. This was incised and drained, but the copious pus was found to be sterile.

At this time some abdominal pain was still present, usually occurring in the right iliac fossa at meal-times. There was also definite tenderness and guarding in the same area. A further laparotomy was performed on Oct. 24, when the terminal ileum was found to be in exactly the same condition as at the previous operation. The affected ileum and the ascending colon were resected. Progress was relatively uneventful, and a radical cure of the fistula in ano was performed on Nov. 21. The sedimentation rate on Nov. 17 was 84 mm. in 2 hours, and on Dec. 11 38 mm. in 2 hours. The patient was discharged very well and free from pain on Dec. 21. Recent communication has been received to the effect that she is very well and has regained weight and strength, but some frequency of stools persists.

Pathological Report

"(1) **Macroscopic:** Approximately 28.5 cm. of ileum and 20.5 cm. of caecum and ascending colon. Ileum forming a U-shaped loop, the two arms about 6 cm. up being joined by fibrous adhesions. Proximal 4 cm. of ileum appears free from disease—beyond this, wall much thickened, mucosa ulcerated, and serous surface rough and deep purple in colour. The ulceration stops at the ileo-caecal valves, but serosa of lowest part of caecum similar to that of ileum and wall thick; ascending colon dilated; mesentery very thick, with numerous enlarged glands. (2) **Microscopic:** Regional ileitis. In addition to the more chronic inflammatory changes there are miliary abscesses in submucosa and mucosa of ileum and caecum. The circular muscle fibres in ileum show fragmentation, and there is oedema of serosa. Chronic inflammation of lymphatic glands. (3) **Skin:** Acute inflammation of granulation tissue in scar with thick purulent exudate."

Case II

The patient, a girl aged 18, was admitted to the Willesden General Hospital on Sept. 5, 1941. She was first seen in the out-patient department in Dec., 1940, but was then unwilling to enter hospital for investigation. There had been loss of weight and anorexia for a year, amenorrhoea for 3 months, pain in the umbilical region for 2 months—the pain occurring during a meal but disappearing in 5 minutes—and alternating diarrhoea and constipation for some months. The only abnormal physical signs at the time were pallor of the mucous membranes and slight tenderness over the right upper rectus.

There was a history of similar trouble at the age of 11, the symptoms lasting for several months. The following is a report from Dr. H. R. Hayes, medical registrar of St. George's Hospital, London, as to the findings at that time: "This patient was admitted on Dec. 12, 1934, with a history of loss of weight and having eaten very little for the previous 4 months. On examination she was very wasted and had a pulse rate of 148. There was no evidence of pulmonary tuberculosis or hyperthyroidism. An electrocardiogram revealed a simple tachycardia. A blood count showed R.B.C. 4,460,000; Hb 65%; W.B.C. 18,400—polymorphs 56%; lymphocytes 41%; monocytes 3%. Bacteriological examination of her stools revealed no pathogenic organisms, cysts, or ova. A diagnosis of anorexia nervosa was made, and she was treated with a simple diet, with moderate improvement."

She was again referred to Willesden General Hospital by her doctor in Sept., 1941, the symptoms having continued and the patient having lost 2 st. in weight. She was very emaciated and ill, and her general appearance, associated with wasting, anorexia, and amenorrhoea, suggested the possibility of anorexia nervosa. (This diagnosis was made before receiving the report from St. George's Hospital.) On examination, however, an indefinite slightly tender swelling was found in the right iliac fossa. There was no diarrhoea at the time, but the bowels were open twice daily and the stools were well formed. The blood pressure was 90/60. The fasting blood sugar was 78 mg. per 100 c.cm., and successive estimations after 50 g. of glucose showed slightly diminished tolerance. A hypochromic anaemia was present: erythrocytes 5,500,000; haemoglobin 58%; colour index 0.5; diameter of red cells 6.5 μ ; leucocytes 10,000—polymorphonuclear cells 67%, lymphocytes 23%, eosinophils 2%, and monocytes 8%. The sedimentation rate was considerably raised—70 mm. in 2 hours. Blood urea was 39 mg. per 100 c.cm. Irregular pyrexia was present, the temperature ranging from 98° to 101° F., and the pulse rate averaging 100. The Mantoux test was positive in 1 in 1,000 dilution. The raised sedimentation rate, pyrexia, and abdominal features were not compatible with the preliminary impression of anorexia nervosa. Roentgenological studies after a barium meal and follow-through examination indicated the correct diagnosis of Crohn's disease, which was confirmed at subsequent operation.

Radiological Report.—"No evidence of any gastric or duodenal organic lesion; the small-gut passage shows a combination of haste and stasis; organic changes are present in the terminal ileum; the caecum is markedly contracted and very tender, and diffuse severe changes of colitis are also present. The differential diagnosis lies between a diffuse ulcerative colitis and Crohn's disease. I think non-specific Crohn's disease is more probable than a tuberculous lesion. The iliac changes are certainly partially obstructive. There is no evidence of any pulmonary lesion."

This patient was seen by one of us (F. W. M. P.) in early October, when she was in a desperately ill condition. Both the physical signs and the x-ray findings agreed with a diagnosis of regional ileocolitis. Although the operative risk was obviously great, it was apparent that if nothing was done she would not live long, and it was therefore decided to perform a laparotomy and a lateral anastomosis.

Operation was carried out on Oct. 14 under gas, oxygen, and ether. An acute form of ileocolitis was discovered, involving the terminal ileum, the ascending colon, and the right quarter of the transverse colon. There were many adhesions between the affected bowel and various portions of ileum. In separating one of these between a piece of ileum and the ascending colon a minute perforation of the latter was observed, and as it was not possible to close this owing to the indurated condition of the bowel, an immediate resection of the affected bowel was done and the ileum was then joined to the transverse colon by end-to-side anastomosis. Towards the close of the operation the condition of the patient became extremely bad, and it seemed doubtful whether it could be possible to return her to the ward alive; but she improved slightly after an intravenous serum drip had been started. The patient, however, never really recovered from the shock of the operation, despite a blood transfusion and continuous rectal infusions of glucose-saline, and she died 3 days later. A post-mortem examination was not made.

Pathological Report

"**Macroscopic:** U-shaped portion of ileum and colon, proximal arm 15 cm., distal arm 11 cm., fibrous adhesions between the two loops extending for about 3 cm. along upper part. Wall of gut thickened up to 1 cm. Very little faecal material in lumen, but a good deal of blood clot. In ileum proximally about 2.5 cm. of normal mucosa, followed by irregular areas of ulceration with overgrowth of mucosa between. Caecum more extensively ulcerated and much con-

tracted. Appendix lying alongside and adherent to ileum—its wall also greatly thickened. Ascending colon ulceration more patchy and mucosa becoming normal in transverse colon. *Microscopical*: Regional ileocolitis. Much ulceration of mucosa with purulent exudate. All casts infiltrated with neutrophil and eosinophil polymorphs, plasma cells, lymphocytes, and histiocytes. A few multinucleated cells present. Much fibrosis of submucosa."

Symptomatology

Whereas Crohn found a slight predominance of males, both our patients were females; their ages were 22 and 18, and in the second case the onset was apparently at the age of 11. The disease occurs most commonly in the third and fourth decades, but has been described in a child aged 7, and is occasionally found in the late-middle-age group. The onset was insidious, and both patients had been ill for some months or years before coming to hospital. Crohn stated that "most of the patients had been ill for several months to two years before coming under observation. During this time the outstanding complaints were diarrhoea, continuous loss of weight, and a progressive anaemia."

In Case II diarrhoea was not a conspicuous feature. In the original description it is stated: "Diarrhoea is usually an outstanding feature, though the number of movements and the intervals of the actions never approach those of a true colitis. The stools are rarely mushy or liquid, and may contain pus, mucus, and streaks of blood."

Recovery from operation in Case I was complicated by an ischio-rectal abscess. Crohn (1939) drew attention to this complication, and wrote: "Perianal, rectal, and recto-vaginal fistulas are the most common type of fistulization present in ileitis." In some cases such fistulas had preceded the more characteristic symptoms by some years, and the advisability of x-ray examination of the ileum in all cases of ischio-rectal abscess was discussed.

With reference to physical examination, Crohn stated that "a moderate-sized mass is usually felt in the lower right iliac region or in the lower mid-abdomen." This was not so in Case I, and was found only in the late stages in Case II: the absence of such a mass does not contraindicate the diagnosis.

Diagnosis

Crohn and his colleagues (1932) named the following disorders in differential diagnosis: non-specific ulcerative colitis, ileo-caecal tuberculosis, appendicitis, actinomycosis, lymphosarcoma, abdominal Hodgkin's disease, carcinoma of terminal ileum. In 1939 Crohn added non-tropical sprue, gastrogenic diarrhoea of achylia gastrica, thyrogenic diarrhoea, undulant fever, and nervous diarrhoea with a psychoneurotic background.

It is interesting that the initial clinical approach to our 2 patients suggested, not necessarily justifiably, the conditions of Addison's disease and anorexia nervosa respectively. In both the systolic blood pressure was under 100 mm. and the degree of wasting considerable. Pigmentation of the skin may occur in avitaminosis of gastro-intestinal origin—e.g., secondary pellagra (Simpson, 1935).

In Case II anorexia, wasting, and amenorrhoea were suggestive of anorexia nervosa (which was also diagnosed independently in 1934); but the rapid pulse, pyrexia, abdominal features, and absence of constipation, as well as the raised sedimentation rate, were sufficient to prevent the diagnosis being sustained. The x-ray examination was conclusive in this patient, and Crohn emphasized its great value. It would seem that a barium meal and follow-through examination are likely to give more positive evidence than a barium enema (see Case I). Crohn stated that the clinical differentiation from non-specific ulcerative colitis is impossible, and the differential diagnosis from this disorder is purely roentgenographic. Ileo-caecal tuberculosis in the adult, in the absence of signs of tuberculous foci elsewhere in the body, Crohn regarded as a much greater rarity than terminal ileitis. The differential diagnosis of this, as of the other conditions he mentions, is ultimately determined by laparotomy and biopsy. Of surgical interest is the persistent sinus after appendicectomy as an indication of an underlying regional ileitis, actinomycosis being another obvious possibility. Here, too, roentgenological investigation and laparotomy may be indicated. In Case II the disease did not stop short at

the ileo-caecal valve, but extended into the caecum and colon, which possibility was contrary to Crohn's original views, but was recognized by him in his 1939 paper. Crohn *et al.* (1932) described the radiological findings as follows: "The barium enema is negative. The barium meal may show (1) distended loops of terminal ileum; (2) delay in motility of the meal through the distal end of the small intestine, with 'puddling' in the ileal loops and 'fuzziness' of outline of the terminal ileum; (3) fistula formation."

Pathology

The following report is extracted from Crohn's (1932) paper:

"Macroscopic.—The terminal ileum is thickened, soggy, and oedematous; the serosa is a blotchy red. The mesentery of the terminal ileum is greatly thickened and contains numerous hyperplastic glands. The earliest lesions consist of oval mucosal ulceration, about 1 c.cm. in diameter, located on the mesenteric border of the small bowel and lying in the long axis of the intestine. The characteristic fully developed hypertrophic process is, as a rule, limited to the distal 25 to 35 mm. (10 to 14 inches) of the terminal ileum. The submucosal and, to a much lesser extent, the muscular layers of the bowel are the seat of marked inflammatory hyperplastic and exudative changes. As a result of these, the wall of the bowel becomes enormously thickened, frequently reaching two or three times its normal density. The lumen of the bowel is greatly encroached upon. In the older phases the exudative reaction is replaced by a fibrostenotic process. A marked feature is the tendency towards perforation into the adjacent colon and caecum, and walled-off abscesses occur as complications. [Added in 1939: "The inflammatory processes in the ileum are not always continuous, the pathological unity often being broken by steep areas. Even the jejunum may be involved."] The stained histological sections showed various degrees of acute, subacute, and chronic inflammation, with variations in the predominance of polymorphonuclear round cells, plasma cells, and fibroplastic elements. In some of the cases the presence of giant cells was quite characteristic, but all guinea-pig inoculation experiments with inoculations of triturated material from mesenteric glands and intestinal wall were negative."

Treatment

The surgical treatment of ileocolitis may be carried out in one-, two-, or multiple-stage operations, and must also vary greatly with the state and progress of the disease and of the patient. The operations performed were: (1) lateral anastomosis with or without exclusion of the lesion; (2) resection with or without exteriorization of the lesion; (3) drainage operations—colostomy and enterostomy, with or without exteriorization of the lesion; and (4) excision of fistulous tracts.

The simplest and least severe form of operation is a lateral anastomosis between healthy ileum and transverse colon. This operation alone may be adequate, and Donald and Brown (1941) reported that it is responsible for cure in 25 to 50% of cases. In a previous case (unreported) one of us (F. W. M. P.) performed a simple side-to-side anastomosis where the last 8 inches of the ileum was found to consist of a contracted tube of scar tissue, and this resulted in complete recovery. It is therefore probably safe to say that when the terminal ileum is sclerosed and obviously quiescent and not complicated by adhesions and fistula formation, a lateral anastomosis may be done with or without transection of the bowel between the stoma and the lesion: it should be noted that Crohn, in the discussion following a paper by Mayo and Judd (1941), strongly advises the former. As a preliminary operation to a resection, an anastomosis is very valuable in that, first, it avoids subjecting a severely ill patient to the risks and shock of a severe operation; and, secondly, it allows the general condition to become improved in the interval between the two operations.

Case I gave an excellent illustration of the immediate benefit derived from a simple short-circuiting operation, almost certainly because of the relief of a mild chronic obstruction alone. It will be seen from the continued high sedimentation rate, the occurrence of an ischio-rectal abscess, and the unchanged character of the affected bowel as found at the second operation, that the anastomosis had had no apparent effect on the primary disease. It is possible, though not certain, that a transection of the ileum might have caused some healing in this case.

Case II illustrates the danger of a primary resection in a seriously ill patient. A two-stage operation had been intended,

but was abandoned because of the complications found during operative procedure.

A resection of the affected ileum, caecum, and part of the colon is obviously the correct method of treatment in all cases except those in which the infection is quiescent, and it now seems to be generally recognized that a two-stage operation is to be preferred. Mayo and Judd (1941) gave the mortality rate as 22% for cases subjected to a one-stage operation, and only 3% when a preliminary short circuit had been done. The delay between stages is open to variation in individual cases, but there is no object in unduly delaying the resection, and we feel that one month might be considered to be the optimum interval. Additional safety may be obtained in a single-stage operation by the exteriorization of the anastomosis or by a temporary enterostomy or colostomy. Mayo and Judd advised leaving out the proximal portion of the transverse colon and using it as a temporary colostomy.

There will be certain advanced types of lesion, complicated by fistula formation and adhesions, which cannot possibly be treated along any set lines. In these cases surgical treatment may be extremely difficult and hazardous, and will probably have to be carried out in multiple stages.

Summary

Two cases of regional ileitis (Crohn's disease) in women aged 22 and 18 are described, especially from the aspects of diagnosis and treatment. The importance of roentgenological examination of the intestinal tract after a barium meal as an aid to diagnosis and the advisability of a two-stage operation are indicated.

We are indebted to Dr. E. Rohan Williams for the radiological reports, and to Dr. G. E. Harre for the pathological reports.

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THE PATHOGENESIS OF PULMONARY TUBERCULOSIS OF THE ADULT TYPE

BY

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Much time and thought have been expended on the pathogenesis and exact method of implantation of the initial lesions of pulmonary tuberculosis of the adult type. I think we should be wiser, so long as our views are in the hypothetical stage, to avoid assumptions and dogmatic statements whenever possible, and to be careful, where assumptions are used, to base as little as possible upon them in the arguments that arise. Another mistake we make is in not taking into account the possibility that there can be more than one answer to the question. Such an attitude limits our endeavours and makes it very difficult to fit the facts at our disposal into our hypotheses without a deal of juggling.

I read in an annotation in the *British Medical Journal* of March 7 (p. 332): "There is evidence that . . . are responsible for the development of bronchogenic tuberculosis (*the common type of pulmonary tuberculosis in adults*). The italics are mine. Here is an assumption which I think is unwarranted. I have read many arguments and studied the data of much research that lead me to suppose that the common type of pulmonary tuberculosis may be bronchogenic in many or even the majority of cases, but I have never found anything approaching a proof that this is a fact, and therefore to build up an argument on the assumption that it is unreasonable and dangerous. Those who have studied the published work on the subject will be able to pick out other dangerously used assumptions like the instance I have given.

It is impossible to fix a truth in the scientific field of knowledge. A hypothesis that satisfies the facts passes into accepted

theory, and the theory holds good and must be accepted as truth just so long as no fresh facts come to light which prove it wrong. It is essential in trying to build a hypothesis to explain the pathogenesis of pulmonary tuberculosis that such a hypothesis must be asked to satisfy facts only, and although assumptions must be used in its structure it should not be based upon them.

Accepted Facts

The following are the facts which I believe are accepted by all students of the subject:

1. The majority of the urban population and a large proportion of the rural population are infected by tuberculosis by the age of 30.
2. Pulmonary tuberculosis of the adult type is not the direct result of a primary infection, although in some cases it may follow very closely on its heels.
3. The lesion resulting from a primary infection, if in the lung (Ghon's focus), is due to an inhalation infection. It may be situated in any part of the lung tissue, but the greater number are found in the right middle and lower and left lower lobes.
4. The early lesion of adult-type pulmonary tuberculosis may appear in any part of the lung, but the overwhelming majority are found in the upper thirds of the upper lobes and more often in the right lung than in the left.
5. When examining unselected samples of the population and unselected samples of contacts, adult-type pulmonary tuberculosis is found ten times more frequently among the contacts. The figures are roughly 0.5% and 5%.

It is tempting to add other "facts," but I have not, as they are facts only to me or to a restricted circle of students, and have not been generally accepted; they must therefore fall into the category of assumptions.

Questions to be Answered

The questions the hypothesis must answer are: (1) Why and how does a person get adult-type pulmonary tuberculosis? The possibilities are (a) by exogenous superinfection, (b) by endogenous exacerbation, (c) by a combination of (a) and (b). (2) By what route does the tubercle bacillus reach the site of the initial lesion of this type of pulmonary tuberculosis—by the respiratory tract, by the blood stream, or by the lymph stream?

Facts Nos. 1, 2, and 5 force the answer to the first part of the first question. Adult-type pulmonary tuberculosis is found in those persons who have been previously infected and is favoured by close contact with persons suffering from pulmonary tuberculosis with positive sputum—that is to say, by superinfection.

The three subsidiary questions to No. 1 and question No. 2 are more complicated, and are so bound up with one another that it is difficult to take them separately; they must be discussed together.

The simplest answer to the remaining question would be that in close contact with sputum-positive cases tubercle bacilli are inhaled in sputum droplets and dust and pass via the respiratory passage to the lung and there set up their characteristic lesions. But this simple answer does not satisfy the facts. Indeed, if it was so simple as that the new lesions would be multiple in most cases and have the same distribution as Ghon foci, and the incidence of the disease among contacts would probably be nearer 100% than 10%.

Ghon foci are definitely inhalation infections, and their distribution in the lungs must therefore give us information on the mechanism and results of inhalation infections. Ghon foci are found in either lung and distributed fairly impartially in all lobes, but the sites of election are the right middle and lower and the left lower lobes. This seems to contradict Bannen's (1942) assertion that an inhalation infection should pass most easily and frequently into the right upper lobe. The fact that an abnormal oily liquid (lipiodol) artificially introduced into the respiratory passages is usually coughed into the bronchus of the right upper lobe is not a conclusive argument. It is an experimental finding which it is dangerous to assume may be repeated under natural conditions. There is a great difference between a blob of lipiodol artificially introduced into the trachea and the 10 μ diameter droplet naturally inhaled (Jacobs, 1941). Bannen states that radiologically (presumably)