THE ELIMINATION OF THE CHRONIC ALIMENTARY ENTERIC CARRIER STATE.

BY

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S E C T I O N 1.

Introduction.

The problem in Bellsdyke Hospital.

The surgical treatment of the first carrier.

THE ELIMINATION OF THE CHRONIC ALIMENTARY ENTERIC CARRIER STATE.

"The problem of a typhoid carrier in a mental hospital is one that must continually subject the authorities to a certain amount of anxiety and particularly that of the ambulatory or undetected clinical case ---- Despite the variety of medical and surgical procedures that have been advocated to rid the individual of his carrier condition and despite the introduction of chloramphenicol it would appear that the treatment of the carrier state in typhoid fever still has to be solved." (Douglas & Hubbard 1951).

"In suitable cases operative treatment directed towards the gall-bladder or the urinary tract which is the only hopeful therapeutic procedure would directly benefit the individual as well as the community." (Browning et al. 1933).

"Attempts to cure the chronic typhoid carrier by removal of the gall-bladder presuppose that this organ contains the only focus of infection in the body. For this belief there is no histological evidence. It is doubtful whether much hope of permanent cure can be offered to the chronic carriers by cholecystectomy. It is more than probable that before long an efficacious chemotherapeutic remedy will be discovered." (Harold 1948).

"Infection of the gall-bladder is one of the most important features of the chronic typhoid carrier state but cholecystectomy is not uniformly successful." (Rumball & Moore, 1949).

"The case of the typhoid carrier presents a curious problem in preventive surgery." (Aird 1949).

The problem of the typhoid carrier is one which has exercised many penetrating minds and which has evoked a very considerable quantity of work, thought, discussion,

compassion and a sizable literature over the last half century. The quotations above recorded illustrate some of the conflicting views which have been put forward in recent years regarding the efficacy of treatment. In a country like Scotland, where standards of health and hygiene are high, the relatively small nidi of enteric carriers probably represent the last stronghold of a disease which in former years has taken its toll of human life and suffering. In the world at large, however, and in particular in the relatively underdeveloped countries, the problem considered as a whole, must still be a vast one.

In spite of the plethora of chemotherapeutic and antibiotic agents which have been made available to us in the past twenty years there is still no certain remedy for the majority of these unfortunates. As will be shown, their condition is a danger not only to the community, but to themselves, in the form of restriction, anxiety, and painful and even potentially fatal disease.

The attention of the writer was first drawn to the carrier problem in the course of surgical practice in Bellsdyke Mental Hospital, Larbert, in 1954. In that hospital there was a nidus of nine alimentary enteric carriers - eight faecal excretors of S. paratyphi B. and

one mixed alimentary carrier excreting intermittently S. typhi and S. paratyphi B. Eight of these carriers had been discovered by the public health authorities during an intensive investigation in 1951 - six from a building know as "Succursal Block" and two from another known as "Main Building". This investigation, which included a very large number of Widal tests and bacteriological examinations of stools, drains, food and kitchen apparatus, was undertaken because of an outbreak of febrile illnesses. On 12th May, 1956 the ninth carrier - a faecal excretor of S. paratyphi B. - was admitted from Gogarburn Hospital, Edinburgh.

The nine carriers were isolated as the sole inmates of a thirty-bedded ward to which they were almost completely confined until 1953 when a more progressive policy was laid down by the new Medical Superintendent, Dr. Allan P. Russell. Thereafter they were allowed a radio and a television set and diversional therapy was instituted. They were, however, perforce excluded from all communal social intercourse and all forms of group therapy and rehabilitation. These restrictions were no doubt responsible for considerable frustration and anxiety and they precluded any advancement in their status within the hospital community. Although it seemed unlikely from the psychiatric point of view that any of the patients would ever progress to become useful members

of the community there was little chance of making any proper assessment or advancement as long as they were so confined.

In addition to this they formed a pocket of potential disease not only within the hospital confines but also outwith its walls. That this was so, and that the infecting organism was a virulent one was shown in 1954 when a Nursing Assistant, S.A., developed overt enteric fever while on holiday in Ireland. S.A. was on night duty in the carrier ward (Hut A.5.) from 23rd September, 1953 to 23rd October, 1953. While on holiday in Dublin from 8th November, 1953 to 14th February, 1954 he was ill with paratyphoid fever.

In 1954 the question of surgical treatment for the carrier group was discussed. A study of the standard works and some of the recent literature left one with mixed feelings about the possible benefits of surgery and no action was taken, but in 1956 one of the patients (M.S.) developed an acute illness which required urgent surgery and which at the same time demonstrated quite clearly that enteric carriers are a danger not only to the community but also to themselves, and that the complications of the carrier state may be extremely serious and even possibly fatal.

The detailed history of this patient and the treatment which he was given are set out over leaf.

CASE No. 1. (M.S. Male, Present age 51.)

This patient was admitted from the Male Succursal Block to the Carrier Ward (Hut A.5.) on 22nd September, 1951, as an enteric carrier, as a result of the public health survey.

On 17th October, 1956, he had an acute episode of abdominal pain and nausea and he vomited once. The tongue was found to be furred and the temperature was 101.4°F. Tenderness was noted over the gall-bladder but the liver was not enlarged. There was no jaundice. On the following day his temperature rose to 103.6°F. but by 13th November, 1956, he was quite well again and had no further complaint of abdominal pain.

On 28th January, 1957 he again began to complain of abdominal pain and the tongue became once more furred. On this occasion his temperature was not elevated but he was, as before, tender over the gall-bladder. A course of achromycin was instituted. On the following day, conjunctival icterus was noted and on 30th January, 1957, jaundice was quite marked although there was still no rise in temperature. The jaundice persisted and over the next few days he vomited occasionally and complained of anorexia and of severe abdominal pain.

On 4th February, 1957, when he was examined by the writer, jaundice was of a moderate degree. A positive Murphy's sign was elicited but the gall-bladder was not palpable. The achromycin therapy was continued and bile salts and Vitamin K. administered by mouth. Examination of the urine showed the presence of bile. Straight X-ray of the gall-bladder region revealed no abnormality. (See fig. 1) (page 11).

LIVER FUNCTION TESTS.

5.2.57.	Serum bilirubin	6.5mgs. per 100 ml.
	Thymol turbidity	6 units.
	Serum acid phosphatase	37.5 King & Armstrong Units.
	Total proteins	7 gms. per 100 ml.
9.2.57.	Vandeberg reaction	- Direct strong positive.
	Serum bilirubin	10.5 mgms. per 100 ml.
	Thymol turbidity	7 units.
	Serum acid phosphatase	30 King & Armstrong Units.
	Total proteins	7 gms. per 100 ml.

13.2.57. Serum bilirubin 7.2 gms. per 100 ml.

20.2.57. Serum bilirubin 7.8 gms. per 100 ml.

In view of his persistent obstructive jaundice it was decided to undertake laparotomy and the operative findings were as follows:-

THEATRE. 22.2.57. Mr. Main.

ANAESTHESIA. Dr. Stewart. Thiopentone, Flaxedil, Nitrous oxide, Ether. Oxygen.

A right, epigastric, paramedian incision was made and a distorted, fibrotic, sub-acutely inflamed gall-bladder and bile duct system was found buried in dense adhesions. Cholecystectomy and choledochostomy were performed with considerable difficulty. No stones were found.

During the freeing of the adhesions it was noted that the duodenum was firmly fixed to the gall-bladder wall. In separating the two a perforation of the necrotic duodenum occurred. This was sutured in two layers using catgut. The right hepatic duct had probably been partially obstructed by fibrotic adhesions. Appendicectomy was performed. The gall-bladder, specimen of bile and the appendix were sent for bacteriological and histological examination. The incision was closed in layers and a gauze drain was left in the gall-bladder bed.

After operation the achromycin therapy was continued. The gauze drain was removed after forty-eight hours. An intra-venous 5% dextrose drip was set up and four pints were given in the first twenty-four hours. On the following day the blood pressure was well maintained, being 146/58 mms. Hg. The achromycin therapy had to be discontinued because of bilious vomiting. Prophylactic penicillin of procaine type 500,000 units b.d. was instituted.

On the following day, vomiting of bile stained fluid continued and the blood pressure dropped to 118/84 mms. Hg. Abdominal distention appeared, but later on the same day flatus was passed per rectum. The vomiting ceased, but his general circulatory state deteriorated and the blood pressure fell further to 104/58 mms. Hg.

On the following day, (25.2.57) the intra-venous drip was set up once more since he was somewhat dehydrated.

5% dextrose (3½ pints) and normal saline (1 pint) were given rapidly. A course of intra-muscular hydrocortisone 25 mgms. daily was instituted. The temperature on that day was 99.2oF. On 26th February, 1957, the intra-venous drip and intra-muscular hydrocortisone were continued. The blood pressure again fell and prednisolone 15 mgs. intra-venously was given in the drip. Thereafter saline (2 pints) and dextrose (4 pints) were given in the next twenty-four hours. The wound began to discharge purulent material from which S. paratyphi B. was isolated.

On 28th February, 1957, the blood pressure was 116/68 mms. Hg. and a collapse was noted at the right lung base. Air entry at both bases was poor and therefore the intra-venous drip was stopped.

When seen on 1st March, 1957, the patient had collapsed over-night and the temperature had risen to 99.8°F. The dose of hydrocortisone was doubled and oral terramycin therapy, 250 mgms. six hourly was started. Because of a further fall in blood pressure, intra-venous therapy was again necessary and the opportunity was taken to give a second 15 mgms. of prednisolone intra-venously. Plasma (1 pint) was added to the daily intake of intra-venous fluid.

On 5th March, 1957, the patient developed a biliary fistula which was probably the result of the giving way of the necrotic duodenum which was perforated at operation and re-sutured. The "T"-tube did not drain satisfactorily and was removed. Skin excoriation became difficult. Continuous suction with a catheter failed to effect adequate drainage.

On 9th March, 1957, abdominal distention became very marked and surgical emphysema of the scrotum, abdominal wall and chest wall appeared. On percussion, the abdomen was very tympanitic and it was felt that there was a distinct possibility of tension pneumo-peritoneum. This was confirmed when the abdominal wall was explored by lumbar puncture needle. A considerable amount of gas was released from the left upper quadrant and the abdominal distention subsided. Thereafter his convalescence was uninterrupted.

On 10th March, 1957, intra-venous therapy was finally stopped.

On 15th March, 1957, a swab from the wound showed B. Proteus only, sensitive to streptomycin and achromycin. The course of terramycin was discontinued, and streptomycin therapy ½ grm. b.d. instituted and continued for one month.

On 10th April, 1957, X-ray showed that the right diaphragm was elevated and that inflammatory changes were still present at the right lung base. There was no evidence, however, of sub-diaphragmatic accumulation of air and no definite evidence of sub-phrenic abscess. Some gaseous fullness was noted in the small bowel coils.

On 16th May, 1957, there was a single elevation of temperature to 100.6°F. but there were no significant findings. By this date the patient was up and about and having physiotherapy.

On 9th July, 1957, he was seen again and his general condition was excellent. There was no trace of jaundice.

HISTOLOGY. The histological examination of the excised gall-bladder showed the gross and microscopic features of highly-acute-on-chronic cholecystitis. A fair thickness of mucosa was left in places though some desquamation had occurred. The mucosa was all densely infiltrated with mainly chronic inflammatory cells. The severity of the reaction was not uniform. (See discussion on histology page 167).

BACTERIOLOGY.

Culture of the gall-bladder, gall-bladder bile, appendix and common bile-duct bile all gave a growth of S. paratyphi B.

BLOOD FINDINGS. 26.1.54.

Hb.	94%	P.C.V.	44%
RBC.	4,000,000 per cu.mm.	M.C.V.	94 c.u.
		M.C.H.C.	33%

BLOOD GROUP. A.B.O. Group A. Rhesus Positive.

CASE No. 1 PATIENT M.S.

FIG.1.

STRAIGHT X-RAY OF GALLBLADDER:- No evidence of stone.

RECORD OF POSITIVE AND NEGATIVE STOOLS FROM JANUARY 1956, UNTIL THE PRESENT TIME.

Patient M.S.

It will be seen from the record opposite that this patient, who was a pure faecal excretor of S. paratyphi B., showed positive stools for four months after cholecystectomy and appendicectomy. Thereafter the stools became persistently negative and have remained so until the present time. It is significant that his post-operative environment was not changed and that he continued to live in the isolation ward with the eight other carriers who continued to excrete the organisms.

SULPHAGUANIDINE (24 gms.) →

CHOLECYSTECTOMY 22/2/57.

NEOMYCIN (20 gms.) →

NEOMYCIN (20 gms.) →

NEOMYCIN (42 gms.) →

Jan.	'56	+
Feb.	"	+
Mar.	"	+
Apr.	"	-
May	"	-
June	"	+
July	"	+
Aug.	"	+
Sept.	"	+
Oct.	"	+
Nov.	"	+
Dec.	"	+
Jan.	'57	+
Feb.	"	+
Mar.	"	+
Apr.	"	+
May	"	+
June	"	+
July	"	-
Aug.	"	-
Sept.	"	-
Oct.	"	-
Nov.	"	-
Dec.	"	-
Jan.	'58	-
Feb.	"	-
Mar.	"	-
Apr.	"	-
May	"	-
June	"	-
July	"	-
Aug.	"	-
Sept.	"	-
Oct.	"	-
Nov.	"	-
Dec.	"	-
Jan.	'59	-
Feb.	"	-
Mar.	"	
Apr.	"	
May	"	
June	"	
July	"	
Aug.	"	
Sept.	"	
Oct.	"	
Nov.	"	
Dec.	"	

Even by the most rigid standards, therefore, his carrier state must be considered to have been eliminated.

NOTE 1. Duodenal intubation for diagnostic purposes was not carried out.

CRITERION SUGGESTED FOR VINDICATION OF CURE.	
Minimum follow-up period after cessation of treatment. (2-weekly cultures).	12 MONTHS. (until Oct., 1959).

Note 2. The following courses of drugs were given to this patient.

From 10.5.52,	to	2.10.53,	Sulphaguanidine	12,506 gms.
From 18.10.56,	to	20.10.56,	Sulphasuxidine	24 gms.

Neither of these two chemotherapeutic agents appears to have had any significant effect on the carrier condition.

The pre and post-operative antibiotic therapy is noted above in the case history.

Courses of oral neomycin were given in September and December 1957 and October 1958 totalling 82 gms. He was given this antibiotic in common with all other carriers at a time when he was not excreting organisms.

In view of the successful outcome of this case, further consideration was given to the whole problem of the nidus of carriers and the writer decided to carry out cholecystectomy, if possible, on all the remaining carriers.

Arrangements were made for radiological, biochemical and histological studies. The results of these studies are set out in the detailed case-histories which follow and are analysed in a later section.

S E C T I O N 11.

Surgical treatment of the remaining eight carriers.

Facilities available.

Precautions taken.

Case histories.

Post-operative precautions.

Record of urinary excretion of enteric organisms by the nine carriers.

SURGICAL TREATMENT OF THE REMAINING EIGHT CARRIERS.

FACILITIES AVAILABLE AT BELLSDYKE MENTAL HOSPITAL.

In this hospital we have gradually assembled an adequate X-ray Department and well-equipped operating theatre, over the past few years, which are capable of dealing with most of the surgical problems which arise in the hospital and where incidentally frontal leucotomies are carried out by the writer for a considerable number of the mental hospitals in central and west Scotland. The co-operation of the Medical Superintendent, Dr. Allan P. Russell, and the Matron, Miss J.G. Ford, and their staffs has been complete. The work of the theatre assistant Mr. P. Daly cannot be too highly praised.

PRECAUTIONS TAKEN TO PREVENT DISSEMINATION OF INFECTION.

Before carrying out the proposed operative treatment and investigations, consideration was given to the possibility of a spread of infection to other patients and staff as a result of movement of the carriers, intimate handling of the patients and the possible contamination of the instruments and apparatus.

The following precautionary measures were therefore taken.

1) HOSPITAL VAN. The hospital van rather than the ambulance was used for the transport of patients and on the days on which it was used for this purpose no other tasks were assigned to it. At the end of each day the interior was thoroughly washed down with 5% Deosan.

2) DURING THE X-RAY STUDIES. The X-ray table was covered with inexpensive plastic material which was subsequently destroyed. Walls and floors were washed down with Deosan. All equipment not required in the department was removed.

3) PATIENTS WERE TAKEN DIRECTLY TO THEATRE from the isolation ward (Hut A.5.) and when the anaesthetist was satisfied that the cough and swallowing reflexes had recovered, they were returned to Hut A.5. where post-operative treatment was carried out.

4) THEATRE TECHNIQUE.

   a) All equipment not likely to be required was removed from theatre.

   b) During the operating sessions, no linen, gowns, or gloves, were allowed to leave the theatre. They were instead soaked in 5% Deosan solution overnight before laundering.

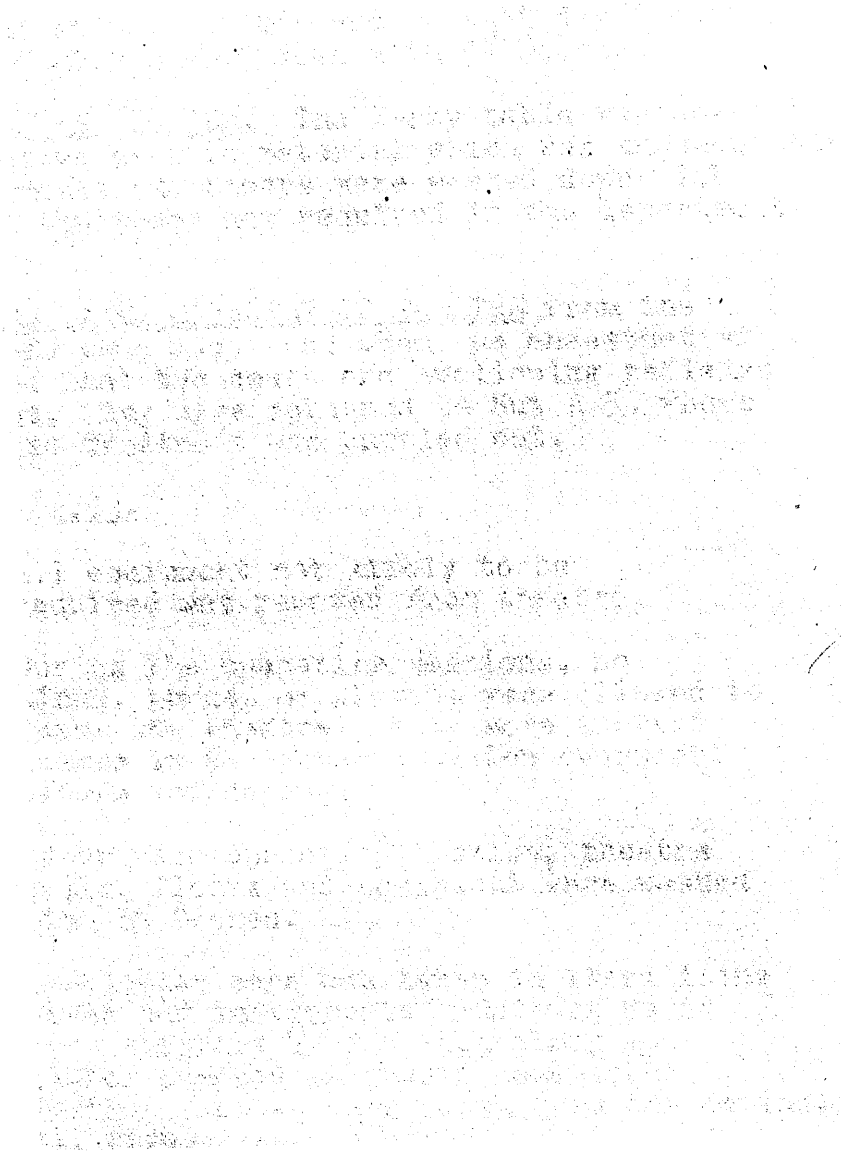
   c) After each operating session, theatre walls, floors and equipment were washed with 5% Deosan.

   d) Particular care was taken in sterilising linen and instruments. Culture media were supplied by the laboratory and plates exposed in theatre overnight. Further samples were taken from the drains. All results were negative.

5) STAFFING. A special staff was appointed to nurse the patients in isolation.

6) IMMUNISATION OF STAFF. T.A.B. inoculations (2 injections) were given to the Staff as undernoted.

Dr. J. Hay, Medical Officer in Charge of the Ward.
Charge Nurse P. Daly, Theatre Assistant.
Nurses:- D. Taylor, E. Beinek, J. Bishop, J. Mincher and J. Grant.



CASE HISTORIES OF THE REMAINING EIGHT CARRIERS TREATED BY OPERATION.

CASE No. 2 (J.C. Male, Present age 52)

This patient was admitted to Hut A.5 from the Male Succursal Block on 8th September, 1951, as a Paratyphoid B. carrier.

He was apparently well but on 22nd April, 1954, he was noted to have a rise of temperature to 104°F. and a corresponding rise in pulse rate. He became jaundiced and it was noted in the case record that his urine was dark. On the basis of the urinary findings, he was considered to have infective hepatitis but it seems that cholangitis was a much more likely explanation. By 21st May, 1954, his jaundice had cleared and he had made a good recovery being up and about again. Thereafter he remained well.

Chest X-ray on 18th April, 1957, showed chronic interstitial fibrosis in the right mid and lower zones.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver function tests.

Serum bilirubin	0.8 mgs. per 100 ml.
Thymol turbidity	3 units.
Serum alkaline phosphatase	8 King & Armstrong units.
Total proteins	7 gms. per 100 ml.
Blood urea	20 mgms. per 100 ml.

Blood findings.

Blood Group A.B.O. Group O. Rhesus Positive.

Hb.	100%	Polymorphs	60%
WBC.	7,200 per cu.mm.	Lymphocytes	35%
		Monocytes	2%
		Eosinophils	3%

Radiological Findings.

Oral cholecystography. (See Fig. 2)

There was inadequate visualisation of the gall-bladder and there appeared to be little evidence of function. Degenerative arthritic changes were noted in the lumbar spine.

Intra-venous cholecystography. (See Fig. 3)

Following intra-venous injection of biligrafin the gall-bladder, hepatic ducts and common bile duct were outlined. A dense ovoid shadow was defined half an hour following injection and in the remaining series it was doubtfully a gall-bladder shadow but the appearances were not entirely conclusive.

Chest X-ray.

This showed no change in the appearances from 1954. Chronic interstitial fibrosis was noted surrounding the right hilar root and extending into the right mid zone.

Operative Findings.

Theatre. 21.7.58. Mr. Main. Anaesthesia. Dr. Beaton. Flaxedil, Nitrous oxide, Oxygen, Fluothane.

A right, epigastric, vertical, rectus-splitting incision was made and a small, fibrotic, "intra-hepatic" gallbladder was found. It was embedded in adhesions and contained one stone. The gall-bladder had obviously been the seat of fairly acute and persistent infection. Cholecystectomy was performed with considerable difficulty. The common bile duct was grossly distended but this was probably compensatory. It was opened and drained by "T" tube. No stones were found within it. Specimens of bile from the gall-bladder and common bile-duct were sent for bacteriological examination. A Penrose drain was left in the gall-bladder bed. The wound was then closed in layers.

Convalescence following the operation was uneventful.

CASE No. 2. PATIENT. J.C.

FIG. 2.

ORAL CHOLECYSTOGRAM:- Inadequate visualisation of the gallbladder. Little evidence of function.

FIG. 3. CASE No. 2 PATIENT J.C.

INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder, hepatic ducts and common bile-duct outlined. Gallbladder shadow doubtful.

FIG. 3. CASE No. 2 PATIENT J.C.

INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder, hepatic ducts and common bile-duct outlined. Gallbladder shadow doubtful.

Bacteriological findings.

Culture of gall-bladder bile	S. Paratyphi B. isolated.
Culture of common bile duct bile	S. Paratyphi B. isolated.

Further cultures of "T"-tube bile were obtained on 1st August, 1958, and 4th August, 1958 and S. Paratyphi B. was isolated from both.

The "T"-tube was removed on the fourteenth post-operative day.

Pathological Findings. (See photomicrographs and discussion. Section VI.)

On macroscopic examination, the gall-bladder was found to measure 5 x 2.5 cms. It contained one stone at the fundus measuring 2 x 1.5 cms. This stone consisted mainly of cholesterol. The wall of the gall-bladder was thickened and in places the mucosa had been shed.

Microscopic examination confirmed the presence of active, chronic, inflammatory infiltration of the muscularis with degenerative change in the mucosa which was atrophic. The remnants of the mucosa were densely infiltrated by inflammatory cells, the infiltration extending fairly deeply. Sub-serous and sub-mucous fibrosis was noted.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at times noted below.

From 10.5.52	to 2.10.53	Sulphaguanidine,	12,506 gms.
From 19.9.57	to 21.9.57	Neomycin,	20 gms.
From 23.12.57	to 2.1.58	Neomycin,	20 gms.
From 18.9.58	to 1.10.58	Neomycin,	27 gms.
From 4.10.58	to 11.10.58	Neomycin,	15 gms.

RESULTS OF TREATMENT.

This patient was a pure faecal excretor of S. paratyphi B. who showed very frequently positive stool cultures in the pre-operative period. After operation the stool became negative for one month. During the following month (Sept. 1958) a positive culture was obtained. Following a course of neomycin, the stools again became negative and remained so for four months. Although the carrier state was apparently cured, however, the possibility of relapse was predicted on the basis of the results of concurrent investigations and in February 1959, the stool again became positive.

His post-operative investigations, further progress and subsequent treatment are discussed in Section Vll.

Note. With the possible exception of the post-operative neomcyin therapy, drug treatment does not seem to have affected the carrier state.

CASE No. 3. (J.K. Male, Present age 69)

This patient was admitted to Hut A.5 from the Male Succursal Block on 30th August, 1951, as a carrier of S. paratyphi B., the organism having been cultured from his stools.

He apparently remained well until 19th December, 1954, when he developed acute diarrhoea and pyrexia. The stools at that time gave positive S. paratyphi B. cultures.

Physical examination before operation showed that his tongue was clean and moist and his fauces clear. No abdominal abnormality was found. Examination of the cardio-vascular, respiratory and central nervous systems gave normal findings. His blood pressure was 122/80 mms. Hg. Slight oedema of the feet was noted. (A former chest X-ray report - 5.7.54 - showed fibrosis in the upper half of the right lung and in the upper part of the left lung with pleural thickening over the left lung and fibrosis at the left base. It was presumed that the changes were due to old tuberculous infection now inactive.) On 6th June, 1958, definite oedema of both feet was noted, more marked on the right side. Bed rest for three days caused considerable improvement.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver function tests.

Serum bilirubin	1 mg. per 100 ml.
Thymol turbidity	2 units.
Serum alkaline phosphatase	6 King & Armstrong units.
Total proteins	7 gms. per 100 ml.
Blood urea	20 mgms. per 100 ml.

Electrocardiogram.

No obvious abnormality and no contra-indication to operation.

Blood findings.

Blood Group A.B.O. Group A. Rhesus positive.

Hb.	95%	Polymorphs	60%
WBC.	6,400 per cu.mm.	Lymphocytes	37%
		Monocytes	2%
		Eosinophils	1%

Radiological Findings.

Oral cholecystography. (See Fig. 4)

The examination showed little evidence of a functioning gallbladder. No radio-lucent calculi were demonstrated. A dorso-lumbar scoliosis of the spine was noted with osteo-arthritic changes.

Intra-venous cholecystography. (See Fig. 5)

The gall-bladder was outlined and appeared to show satisfactory function.

Chest X-ray.

No change from previous examination.

Operative Findings.

Theatre 28.7.58. Mr. Main. Anaesthesia. Dr. Beaton. Thiopentone, Flaxedil, Nitrous-Oxide, Oxygen, Fluothane.

A right, epigastric, vertical, rectus-splitting incision was made. The gall-bladder was found to be grossly distended and full of facetted stones. The common bile duct was normal. It was aspirated and a specimen of bile sent for bacteriological examination. Cholecystectomy was then performed and a Penrose drain was left in the liver bed. The incision was closed in layers. The gall-bladder was sent for histological examination.

During his post-operative convalescence a left basal collapse developed and a short course of achromycin and crystalline penicillin was given.

On 3rd August, 1958, the patient was found to have developed auricular fibrillation and from time to time there was respiratory distress. No gross cyanosis,

CASE No. 3 PATIENT J.K.

FIG. 4.

ORAL CHOLECYSTOGRAM:- Little evidence of a functioning gallbladder. No radio-lucent calculi.

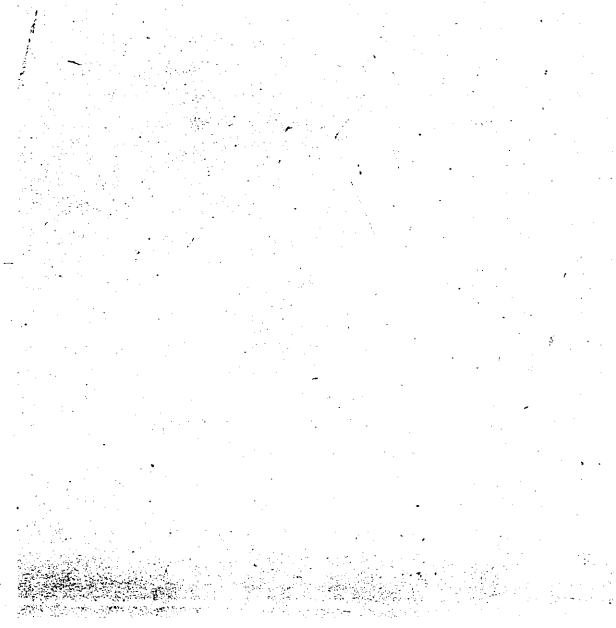
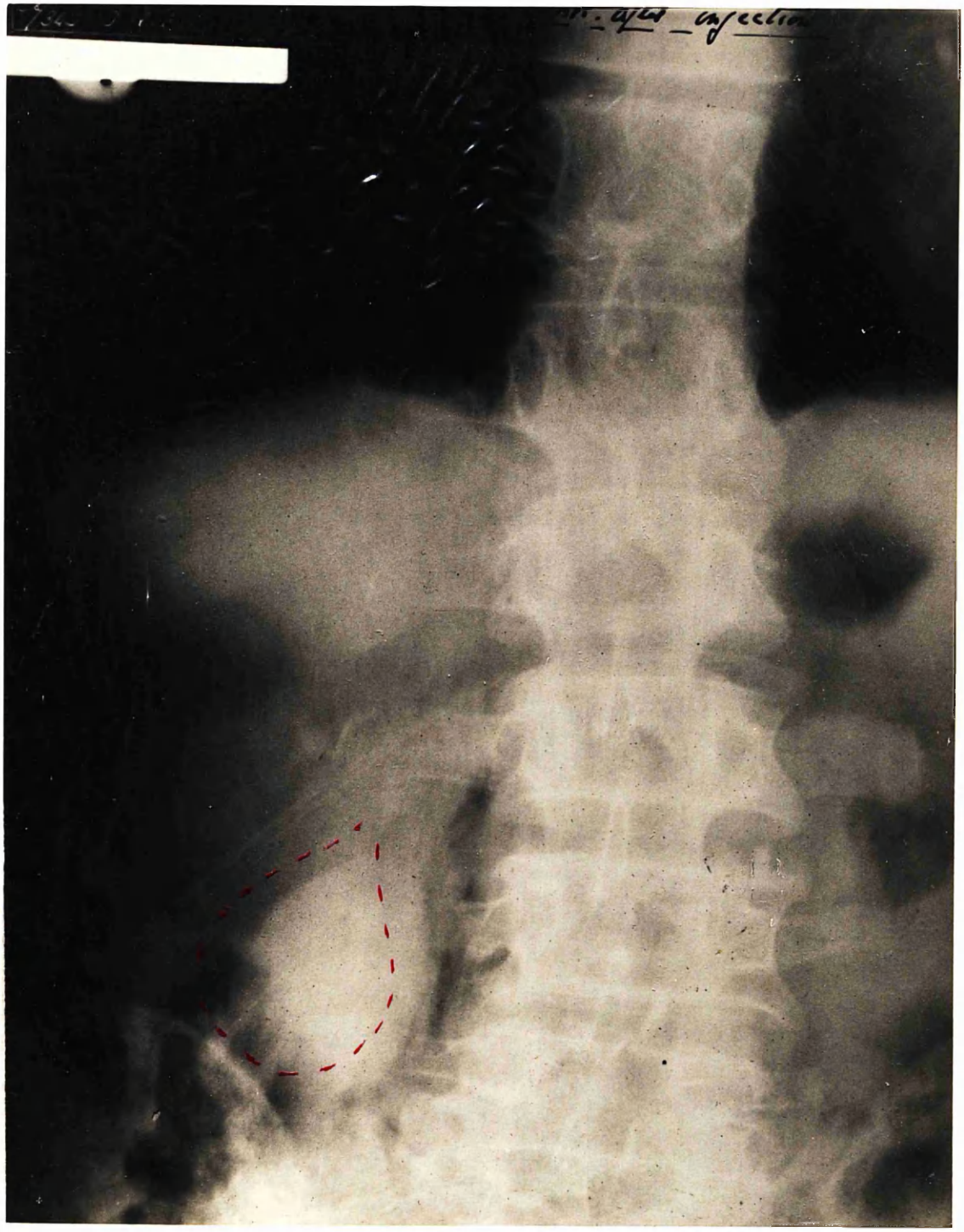


FIG. 5

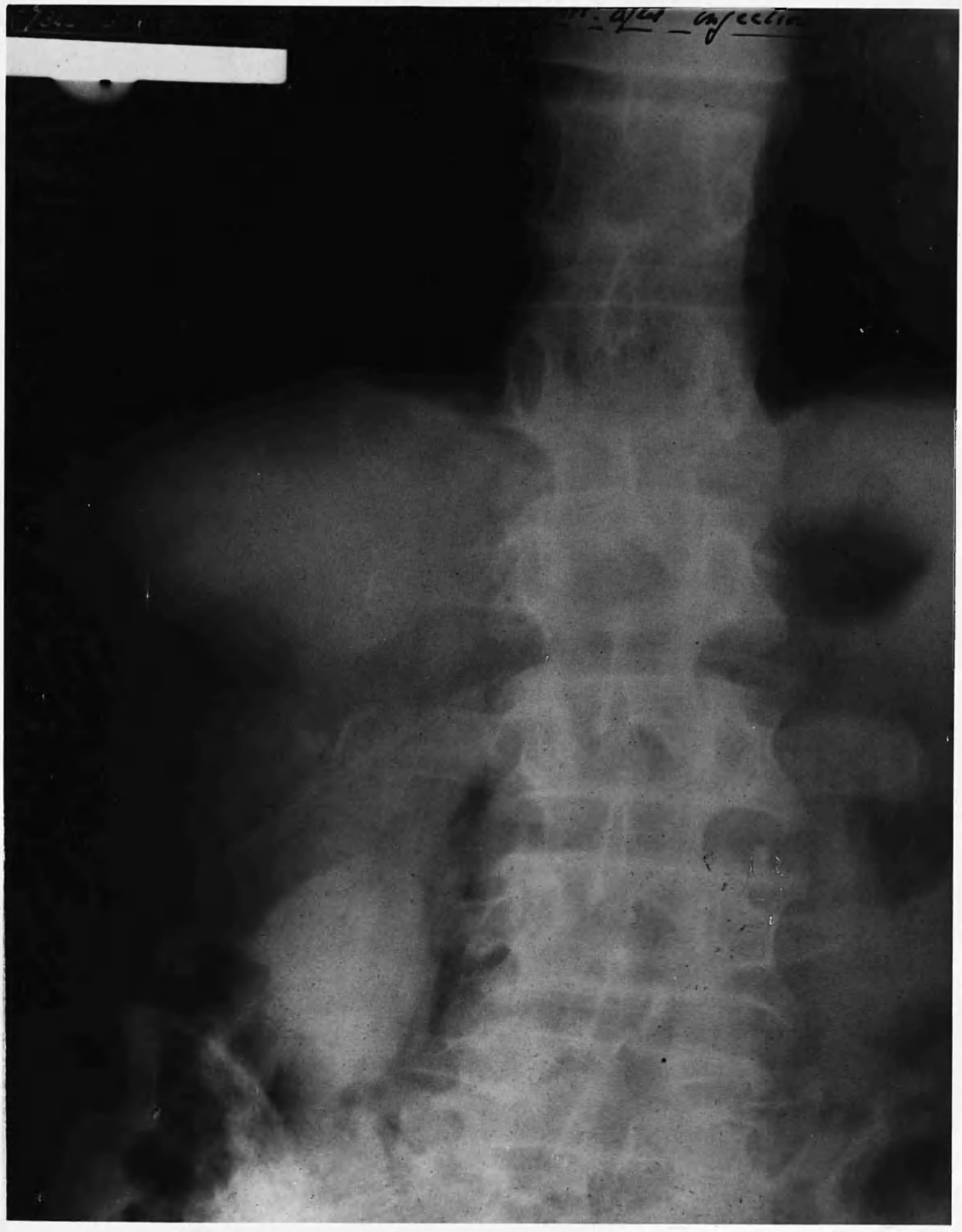
CASE No. 3 PATIENT J.K.



INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder visible. Satisfactory function.

FIG. 5

CASE No. 3 PATIENT J.K.



INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder visible. Satisfactory function.

however, was present. Congestive signs appeared at both lung bases. He was digitalised. Subsequent convalescence was uneventful.

Bacteriological Findings.

Culture of common bile duct bile S. paratyphi B. isolated.

Pathological Findings.

On macroscopic examination, the gall-bladder, was found to be 7 cms. long and 3.5 cms. in diameter. It contained one large cholestrol stone and several small facetted stones. The wall was not thickened but the mucosa was puckered and scarred 7 cms. from the fundus.

On microscopic examination the scarring and infolding of the mucosa was confirmed. The gall-bladder wall was well preserved. Some oedema was noted between muscle bundles and a quite marked diffuse inflammatory infiltrate was seen, especially in the mucous membrane. The appearances were those of chronic cholecystitis and lithiasis.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at times noted below.

From 10.5.52	to	2.10.53	Sulphaguanidine,	12,506 gms.
From 23.10.54	to	28.10.54	Sulphathiazole,	42 gms.
From 12.9.57	to	21.9.57	Neomycin,	20 gms.
From 23.12.57	to	2.1.58	Neomycin,	20 gms.
From 31.7.58	to	3.8.58	Achromycin	4 gms.
From 3.8.58	to	12.8.58	Penicillin	5,400,000 units.
From 18.9.58	to	1.10.58	Neomycin	27 gms.
From 4.10.58	to	11.10.58	Neomycin	15 gms.

RESULTS OF TREATMENT.

This patient was a fairly consistent pure faecal excretor of S. paratyphi B. After a course of neomycin in September 1957, the stool cultures remained negative for a period of five months. (A second course was given in December 1957). The stool, however, showed a further positive culture in February 1958. Cholecystectomy was carried out in July 1958. In September 1958 a positive stool was recorded, but after a further course of oral neomycin the stools again became negative and have remained so until the present time. (6 months).

The post-operative environment was not changed.

It is concluded that this patient's carrier state has been eliminated by cholecystectomy, and neomycin therapy.

CRITERION SUGGESTED FOR VINDICATION OF CONCLUSION.	
Longest recorded excretion-free period before commencement of treatment.	3 MONTHS.
Minimum suggested follow-up period after cessation of treatment. (2-weekly cultures).	12 MONTHS. (until Oct' 1959).

CASE No. 4. (H.McM. Male, Present age 55)

This patient was admitted to Hut A.5 from the Male Succursal Block on 16th October, 1951 as a mixed carrier of S. typhi and S. Paratyphi B., these organisms having been isolated from the stools. He apparently remained well over the years.

Physical examination before operation showed that the tongue was clean and moist and that the fauces were clear. Examination of the cardio-vascular system showed that the pulse was regular and the heart sounds closed. His blood pressure was 98/56 mms. Hg. Examination of the central nervous system and respiratory systems showed no abnormality. Examination of the abdomen showed no tenderness and no abnormal masses.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver function tests.

Serum bilirubin	0.8 mg. per 100 ml.
Thymol turbidity	2 units.
Serum alkaline phosphatase	6 King & Armstrong units.
Total proteins	7 gms. per 100 ml.
Blood urea	25 mgms. per 100 ml.

Blood findings.

Blood Group A.B.O. Group O Rhesus positive.

Hb.	106%	Polymorphs	59%
WBC.	8,100 per cu.mm.	Lymphocytes	37%
		Monocytes	2%
		Eosinophils	2%

Radiological findings.

Oral cholecystography. (See Fig. 6)

At this examination an ill defined shadow was noted in the right hypochondrium which was thought possibly to be gall-bladder outlined by dye but this appearance was somewhat conjectural.

Intra-venous cholecystography. (See Fig. 7)

At this examination a long gall-bladder was delineated filled by dye and containing a small dense stone within the fundus. The common bile-duct was outlined and was normal.

Operative Findings.

Theatre. Mr. Main. 21.7.58.

Anaesthesia. Dr. Beaton. Thiopentone, Flaxedil, Nitrous Oxide, Oxygen, Fluothane.

A right epigastric, vertical, rectus-splitting incision was made. The omentum was found to be adherent to a very large gall-bladder which contained one large stone. It had been the seat of chronic inflammation. The common bile-duct was normal. Bile was aspirated and sent for bacteriological examination. Cholecystectomy was thereafter carried out and the organ was sent for histological examination. The incision was closed in layers and a Penrose drain was left in the liver bed.

Convalescence following the operation was uneventful.

Bacteriological Findings.

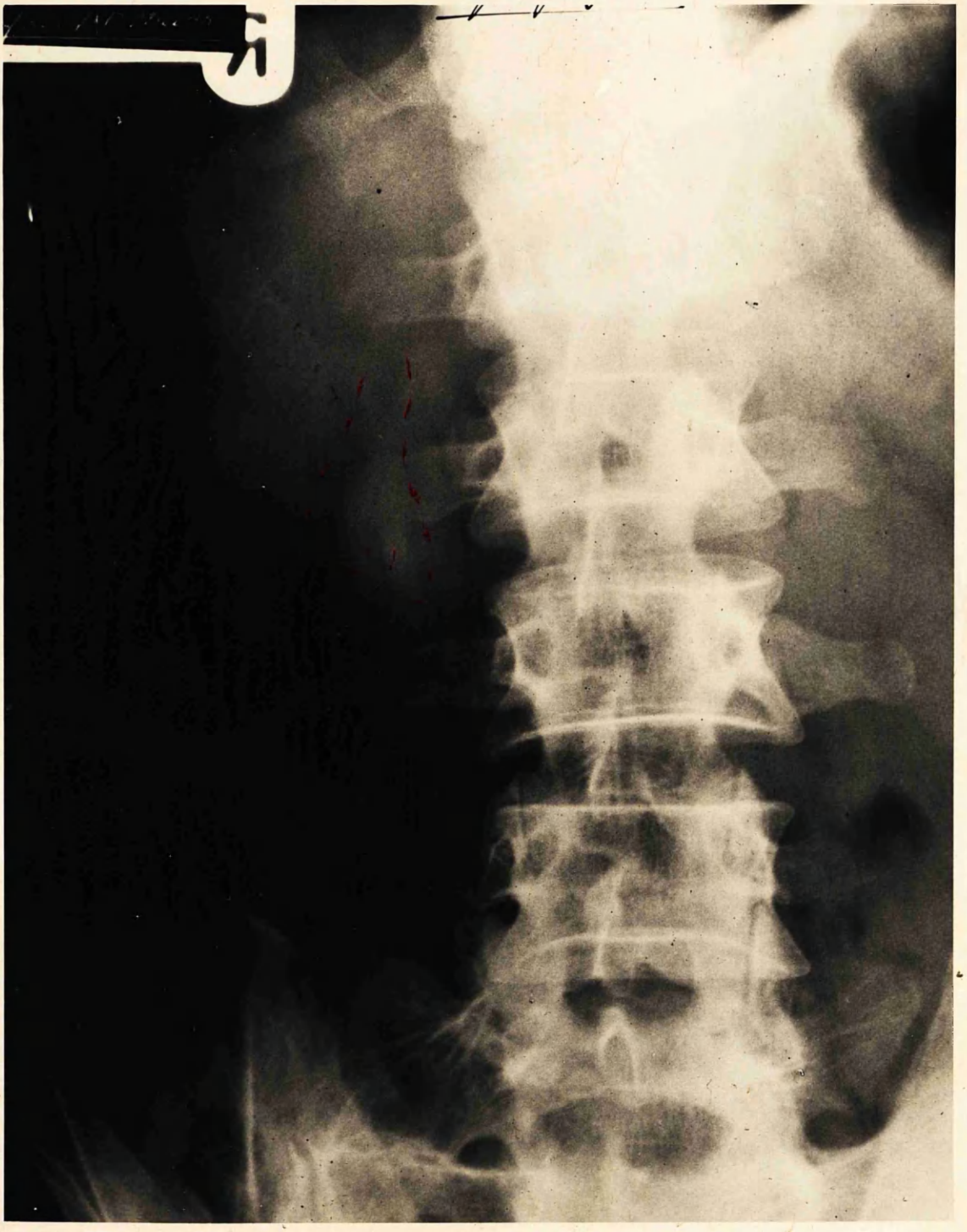
Culture of common bile duct bile. S. paratyphi B. isolated.

Pathological Findings.

On macroscopic examination the gall-bladder was found to measure 10 x 3½ cms. It contained a 3½ x 2 cm. stone consisting mainly of cholesterol. The mucosa of the fundus was smooth but elsewhere appeared normal.

On microscopic examination the mucosa was atrophic. The muscularis had disappeared and was replaced by connective tissue. Foci of inflammatory infiltrate were found in the mucosa indicative of continued infection.

FIG. 6. CASE No. 4 PATIENT H.McM.



ORAL CHOLECYSTOGRAM:- Ill-defined shadow in right hypochondrium, possibly gallbladder. Appearance somewhat conjectural.

FIG. 6. CASE No.4 PATIENT H.McM.

ORAL CHOLECYSTOGRAM:- Ill-defined shadow in right hypochondrium, possibly gallbladder. Appearance somewhat conjectural.

FIG. 7. CASE No. 4 PATIENT H.McM.

INTRA-VENOUS CHOLECYSTOGRAM:- Long gallbladder delineated, filled by dye and containing a small dense stone.

FIG. 7. CASE No. 4 PATIENT H.McM.

INTRA-VENOUS CHOLECYSTOGRAM:- Long gallbladder delineated, filled by dye and containing a small dense stone.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at times noted below.

From 10.5.52	to	2.10.53	Sulphaguanidine,	12,506 gms.
From 12.9.57	to	21.9.57	Neomycin	20 gms.
From 23.12.57	to	2.1.58	Neomycin	20 gms.
From 18.9.58	to	1.10.58	Neomycin	27 gms.
From 4.10.58	to	11.10.58	Neomycin	15 gms.

RESULTS OF TREATMENT.

This patient was an intermittent faecal excretor of enteric organisms. S. typhi and S. paratyphi B. were isolated from the stools with about equal frequency.

It is impossible to say from the record whether pre-operative neomycin therapy had any effect on the excretion of enteric organisms, but it seems unlikely that this was so. Following cholecystectomy the stool cultures became negative and have remained so until the present time. (7 months)

The post-operative neomycin therapy was given to all of the carriers. Since this patient's stool was negative at that time, no conclusion can be drawn regarding the result of the therapy.

It is concluded that this patient's carrier state has been eliminated by cholecystectomy.

CRITERION SUGGESTED FOR VINDICATION OF CONCLUSION.	
Longest recorded excretion-free period before commencement of treatment.	8 MONTHS.
Minimum suggested follow-up period after cessation of treatment. (2-weekly cultures).	24 MONTHS (ends Dec 1960).

CASE No. 5. (D.S. Male. Present age 47)

This patient was admitted to Hut A.5 from the Male Succursal Block on 30th August, 1951, as an S. Paratyphi B. carrier, the organism having been isolated from the stools.

In November 1949 he had been confined to bed with pyrexia, averaging 102°F., for two weeks. Except for some dullness at the right base no physical signs were found. Chest X-ray, however, showed a shadow at the right hilum suggestive of pneumonic consolidation. He was given courses of penicillin and sulphathiazole and appeared to respond. Thereafter he remained well until January 1954, when he complained of a heavy cold and had elevation of temperature, to 104°F. For this he was given penicillin, 500,000 units b.d. He developed auricular fibrillation and was temporarily digitalised.

Physical examination before ~~examination~~ operation showed that the tongue was clean and moist and the fauces clear. Examination of the cardio-vascular system showed that the pulse was regular. The apex beat was found to be in the mid-clavicular line. The heart sounds were closed. His blood pressure was 142/96 mms. Hg. Respiratory system and central nervous system showed no abnormality. Abdominal examination showed no tenderness and no abnormal masses.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver function tests.

Serum bilirubin	0.8 mgs. per 100 ml.
Thymol turbidity	4 units.
Serum alkaline phosphatase	5 King & Armstrong units.
Total proteins	7.5 gms. per 100 ml.
Blood urea	20 gms. per 100 ml.

Blood findings.

Blood Group A.B.O. Group O. Rhesus Positive.

Hb.	106%	Polymorphs	78%
WBC.	16,000 per cu.mm.	Lymphocytes	20%
		Monocytes	1%
		Eosinophils	1%

Radiological findings.

Oral cholecystography. (See Fig. 8)

No opaque calculus was found. Following ingestion of the dye a shadow was defined medially in the right costo-lumbar angle. Unfortunately the shadow was not well defined and the examination was inconclusive.

Intra-venous cholecystography. (See Fig. 9)

The gall-bladder was outlined and showed moderate function. No radio-lucent calculi were demonstrated.

Operative Findings.

Theatre. 28/7/58. Mr. Main. Anaesthesia. Dr. Beaton. Thiopentone, Flaxedil, Nitrous Oxide, Oxygen, Fluothane.

A right, epigastric, vertical, rectus-splitting incision was made. The gall-bladder was found to be enlarged, tense and somewhat adherent but otherwise showed no remarkable abnormality. The common bile-duct was aspirated and a specimen of bile sent for bacteriological examination. Cholecystectomy was performed and the gall-bladder sent for histological examination. The incision was closed in layers and a Penrose drain left in the liver bed.

Convalescence following the operation was uneventful.

Bacteriological findings.

Culture of common bile-duct bile S. Paratyphi B. isolated.

Pathological findings.

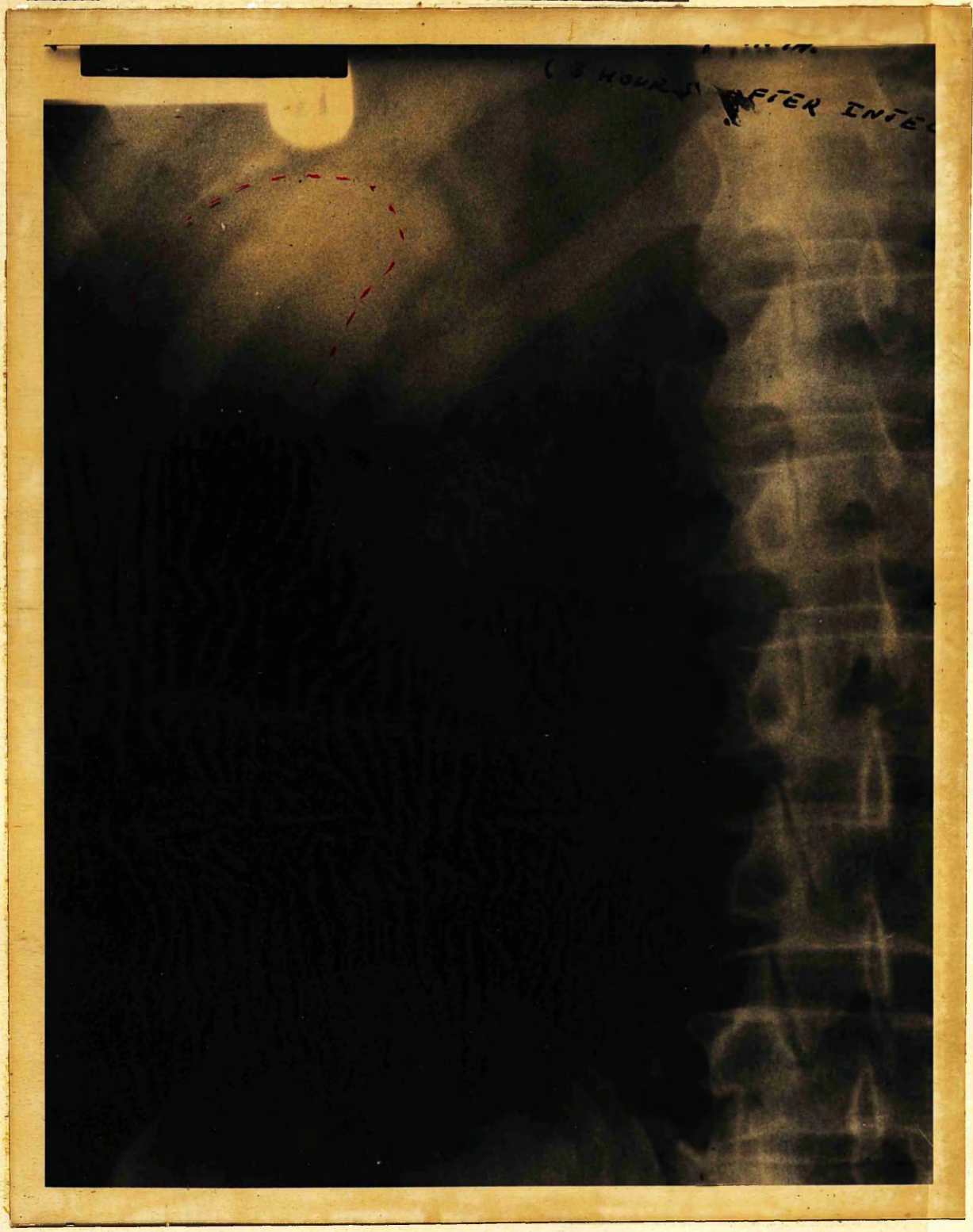
On macroscopic examination the gall-bladder was found to measure 9 x 3.5 cms. It showed some autolysis of the mucosa.

CASE No. 5 PATIENT D.S.

FIG. 8.

ORAL CHOLECYSTOGRAM:- A shadow was defined in the right costo-lumbar angle. Examination inconclusive.

FIG. 9. CASE No. 5 PATIENT D.S.



INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder shadow visible. Moderate function. No radio-lucent calculi.

FIG. 9. CASE No. 5 PATIENT D.S.

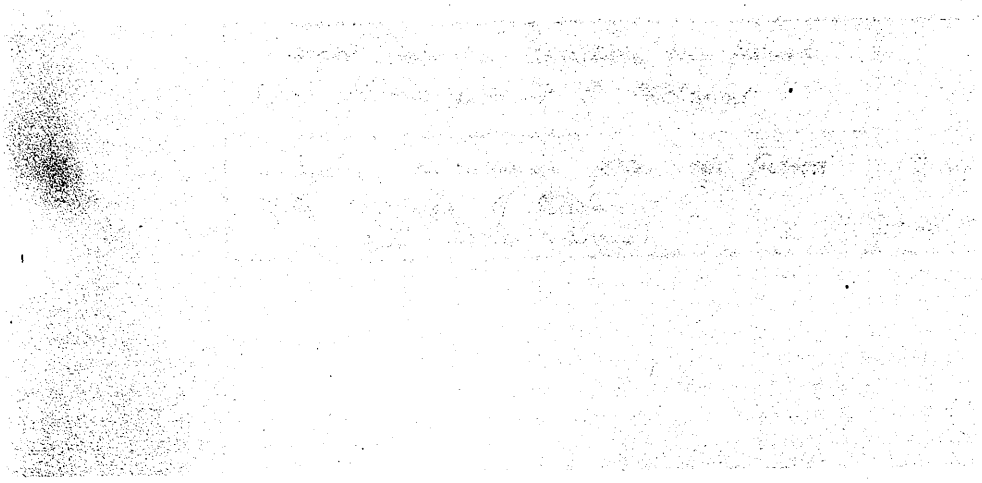
INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder shadow visible. Moderate function. No radio-lucent calculi.

On microscopic examination the wall of the gall-bladder was found to be very vascular and indeed congested. A sprinkling of inflammatory cells were noted in the mucosa spreading deeply via deep crypts. One aggregate of inflammatory cells was noted.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at time noted below.

From 10.5.52	to	2.10.52	Sulphaguanidine,	12,506 gms.
From 27.1.54	to	5.2.54	Penicillin,	9,500,000 units.
From 19.10.55	to	25.10.55	Penicillin,	9,000,000 units.
From 12.9.57	to	21.9.57	Neomycin,	20 gms.
From 23.12.57	to	2.1.58	Neomycin,	20 gms.
From 31.7.58	to	8.8.58	Achromycin,	9 gms.
From 18.9.58	to	1.10.58	Neomycin,	27 gms.
From 4.10.58	to	11.10.58	Neomycin,	15 gms.



RESULTS OF TREATMENT.

This patient was an intermittent faecal excretor of S. paratyphi B. Following courses of oral neomycin in September and December 1957 and cholecystectomy in July 1958, the stool cultures have remained negative until the present time. (7 months since operation).

It is concluded that the carrier state has been eliminated by a combination of neomycin therapy and cholecystectomy.

Note. A post-operative course of neomycin was given in September 1958 to this patient (in common with all other carriers) at a time when stool culture was negative.

CRITERION SUGGESTED FOR VINDICATION OF CONCLUSION.	
Longest recorded excretion-free period before commencement of treatment.	4 MONTHS.
Suggested minimum follow-up period after cessation of treatment. (2-weekly cultures).	12 MONTHS. (until Oct. 1959).

CASE No. 6. (J.Cr. Male. Present age 56)

This patient was admitted to Hut A.5 from the Male Succursal Block on 13th October, 1951, as a S. paratyphi B. carrier, the organism having been isolated from the stools.

He apparently remained well over the years.

Physical examination before operation showed that the tongue was clean and moist and the fauces clear. Examination of the cardio-vascular, respiratory and central nervous systems showed no abnormality. His blood pressure was 116/62 mms. Hg. On abdominal examination there was no tenderness and no abnormal masses.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver function tests.

Serum bilirubin	0.8 mgs. per 100 ml.
Thymol turbidity	2 units.
Serum alkaline phosphatase	12 King & Armstrong units.
Total proteins	6.75 gms. per 100 ml.
Blood urea	20 gms.

Blood findings.

Blood Group A.B.O. Group A. Rhesus negative.

Hb.	112%	Polymorphs	63%
WBC.	7,800 per cu.mm.	Lymphocytes	32%
		Monocytes	3%
		Eosinophils	2%

Radiological Findings.

Oral cholecystography. (See Fig. 10)

This showed a normally functioning gall-bladder. No radio-lucent calculi were demonstrated. Calcified mesenteric glands were noted.

Intra-venous cholecystography.

This examination was therefore not necessary.

Operative Findings.

Theatre. 2.6.58. Mr. Main. Anaesthesia. Dr. Beaton. Thiopentone, Flaxedil, Nitrous Oxide, Oxygen, Fluothane.

A right, epigastric, vertical, rectus-splitting incision was made. Adhesions were noted in the region of Hartmann's Pouch and cystic duct. The gall-bladder was otherwise normal. No stones were found. The common bile-duct was found to be normal in size. It was aspirated and a specimen of bile sent for bacteriological examination. Cholecystectomy was then performed. The gall-bladder was sent for histological examination. The incision was closed in layers without drainage.

Convalescence following operation was uneventful.

Bacteriological Findings.

Culture of common bile-duct bile No growth.

Pathological Findings.

On macroscopic examination the gall-bladder was found to be small measuring 3.25 x 2.5 cms. It showed no feature of special note.

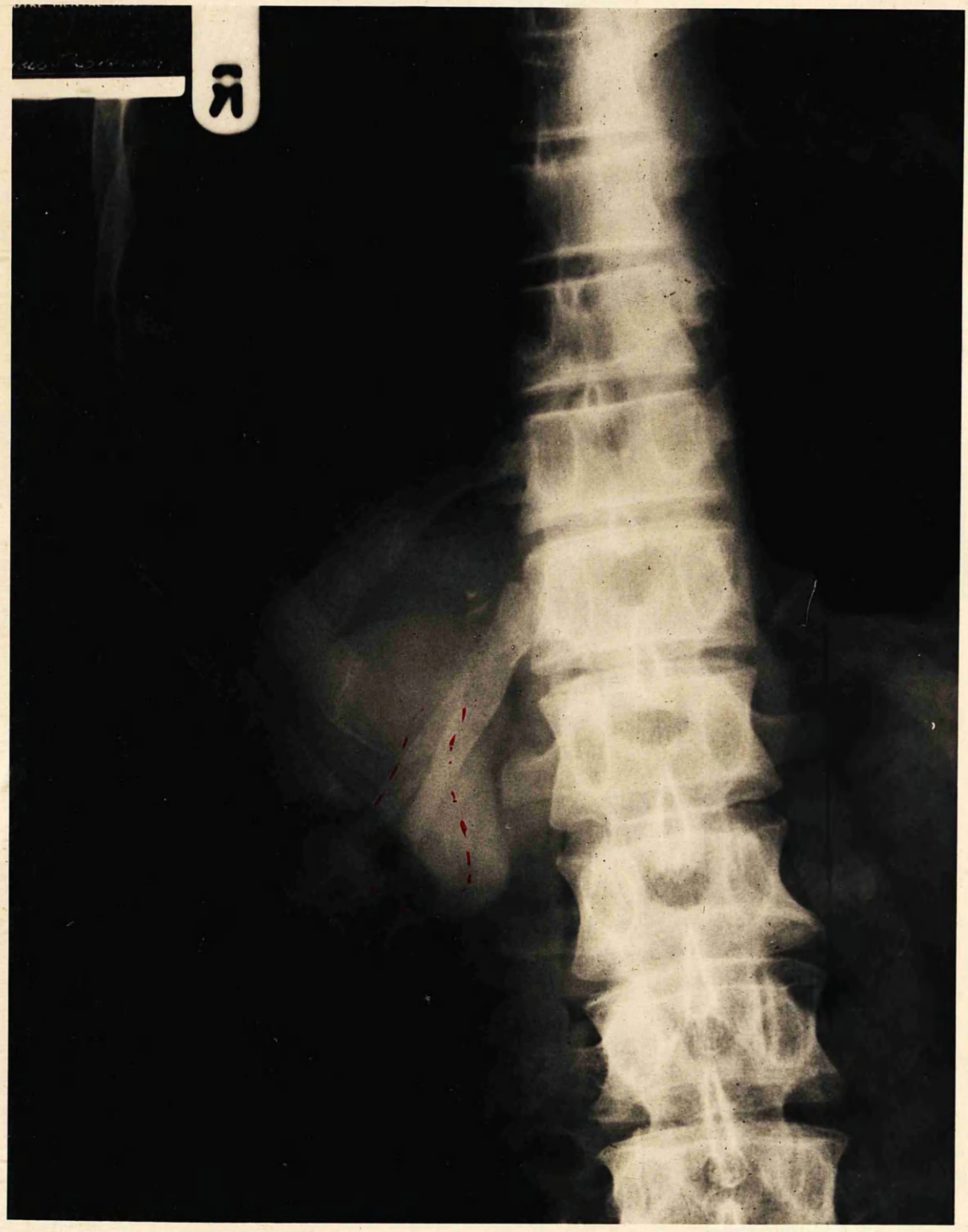
On microscopic examination fibrosis of the sub-mucous and sub-serous coats was noted. There was also slight fibrosis of the muscularis but there was no sign of active inflammation.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at times noted below.

From 10.5.52	to 2.10.53	Sulphaguanidine,	12,506 gms.
From 12.7.57	to 21.9.57	Neomycin	20 gms.
From 23.12.57	to 2.1.58	Neomycin	20 gms.
From 18.9.58	to 1.10.58	Neomycin	27 gms.
From 4.10.58	to 11.10.58	Neomycin	12 gms.

FIG. 10. CASE No. 6 PATIENT J.Cr.



ORAL CHOLECYSTOGRAM:- Normally functioning gall-bladder. No radio-lucent calculi.

FIG. 10. CASE No. 6 PATIENT J.Cr.

ORAL CHOLECYSTOGRAM:- Normally functioning gall-bladder. No radio-lucent calculi.

RESULTS OF TREATMENT.

This patient was an intermittent occasional faecal excretor of S. paratyphi B. Following courses of oral neomycin in September and December 1957 the stools remained negative, but following cholecystectomy in June 1958 two positive cultures were obtained. A further course of neomycin was given in September 1958 and the stools have remained negative until the present time. (7 months from cholecystectomy)

It is concluded that the carrier state has been eliminated by a combination of neomycin therapy and cholecystectomy.

Note. A post-operative course of neomycin was given in September 1958 to this patient (in common with all other carriers) at a time when stool culture was negative.

CRITERION SUGGESTED FOR VINDICATION OF CONCLUSION.	
Longest recorded excretion-free period before commencement of treatment.	8 MONTHS.
Suggested minimum follow-up period after cessation of treatment. (2-weekly cultures).	24 MONTHS. (until Oct' 1960).

CASE No. 7 (T.B. Male. Present age 38)

This patient was admitted to Hut A.5 from the Male Main Building on 30th August, 1951 as a carrier of S. typhi B., the organism having been isolated from his stools.

In July 1951 he was ill with irregular pyrexia. For ten days he complained of abdominal pain. Widal reaction at this time showed agglutination to S. Typhi H. in a titre of 1/2,500. By 19th September, 1957, he had fully recovered. Following this case the Medical Officer of Health carried out his investigation of staff and patients in the Succursal Block and Main Building. As a result the nidus of paratyphoid B. carriers was discovered and measures were taken to have them isolated.

Pre-operative physical examination showed that the tongue was clean and moist and the fauces were clear. Cardio-vascular, respiratory and central nervous systems showed no abnormality. Examination of the abdomen showed no tenderness and there were no abnormal masses.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver Function Tests.

Serum bilirubin	0.2 mgms. per 100 ml.
Thymol turbidity	3 units.
Serum alkaline phosphatase	7 King & Armstrong units.
Total proteins	8.5 gms. per 100 ml.
Blood urea	40 mgms. per 100 ml.

Blood Findings.

Blood Group A.B.O. Group O Rhesus Negative.

Hb.	112%	P.C.V.	48%
RBC.	5,700,000 per cu.mm.	M.C.V.	83%
		M.C.H.C.	34%

Radiological Findings.

Oral cholecystography. (See Fig. 11)

A normally functioning gall-bladder. No radio-lucent calculi were demonstrated.

Intra-venous cholecystography.

This examination was not necessary.

Operative Findings.

Theatre. 2.6.58. Mr. Main. Anaesthesia. Dr. Beaton. Thiopentone, Flaxedil, Nitrous Oxide, Oxygen, Trilene, Pethedine.

A right, epigastric, paramedian incision was made. Adhesions were noted around the base of the gall-bladder. The organ was otherwise normal. The common bile-duct was normal. It was aspirated and a specimen of bile sent for bacteriological examination. Cholecystectomy was then performed and the gall-bladder sent for histological examination. The incision was closed in layers and a Penrose drain left in the liver bed.

After operation he developed temporary retention of urine which yielded to conservative therapy. He had an intermittent pyrexia for a day or two for which he was given a short course of achromycin. Convalescence was otherwise uneventful.

Bacteriological Findings.

Culture of common bile-duct bile — No significant organisms isolated.

Pathological Findings.

On macroscopic examination the gall-bladder was found to be small measuring 5 x 2¼ cms. It was thin-walled.

On microscopic examination the mucosa was found to be thin and a little simplified. The muscularis showed partial fibrosis. There was considered to be some evidence of past inflammatory activity in the gall-bladder but certainly no sign of a recent episode.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at times noted below.

From 10.5.52	to 2.10.53	Sulphaguanidine,	12,506 gms.
From 12.7.57	to 21.9.57	Neomycin	20 gms.
From 23.12.57	to 2.1.58	Neomycin	20 gms.
From 4.6.57	to 12.6.58	Achromycin	7.5 gms.
From 18.9.58	to 1.10.58	Neomycin	27 gms.
From 4.10.58	to 11.10.58	Neomycin	12 gms.

FIG. 11. CASE No. 7 PATIENT T.B.

ORAL CHOLECYSTOGRAM:- Normally functioning gallbladder. No radio-lucent calculi.

FIG. II. CASE No. 7 PATIENT T.B.

ORAL CHOLECYSTOGRAM:- Normally functioning gallbladder. No radio-lucent calculi.

RESULTS OF TREATMENT.

This patient was a very occasional faecal excretor of enteric organisms. It is probable that he was a mixed excretor of S. typhi and S. paratyphi B. Following courses of oral neomycin in September and December 1957 and cholecystectomy in June 1958 the stool cultures have remained negative till the present time. (8 months from cholecystectomy, 17 months in all.)

It is concluded that the carrier state has been eliminated by a combination of neomycin therapy and cholecystectomy.

Note. A post-operative course of neomycin was given in September 1958 to this patient (in common with all other carriers) at a time when stool culture was negative.

CRITERION SUGGESTED FOR VINDICATION OF CONCLUSION.	
Longest recorded excretion-free period before commencement of treatment.	10 MONTHS.
Suggested minimum follow-up period after cessation of treatment. (2-weekly cultures).	24 MONTHS. (until Oct' 1960).

CASE No. 8 (H.McD. Male, Present age 47)

This patient was admitted to Hut A. 5 from the Male Main Building on 30th August, 1951, as a carrier of S. Paratyphi B., the organism having been isolated from the stools.

He remained well over the years.

Pre-operative physical examination showed that the tongue was clean and moist and the fauces clear. Examination of the cardio-vascular, respiratory and central nervous systems showed no abnormality. Abdominal examination showed no tenderness and no abnormal masses were present.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver Function Tests.

Serum bilirubin	0.2 mgms. per 100 ml.
Thymol turbidity	
Serum alkaline phosphatase	9 King & Armstrong units.
Total proteins	8 gms. per 100 ml.
Serum urea	40 mgms. per 100 ml.

Blood Findings.

Blood Group A.B.O. Group O Rhesus Negative.

Hb.	105%	Polymorphs	64%
WBC.	7,200 per cu.mm.	Lymphocytes	35%
		Eosinophils	1%

Radiological Findings.

Oral cholecystography. (See Fig. 12)

No opaque calculus was demonstrated and there was little evidence of a functioning gall-bladder. It is also to be noted, however, that there was little evidence of any dye-stuff in the bowel and it was questioned whether this patient had actually ingested the dye. The examination was therefore inconclusive.

Intra-venous cholecystography. (See Fig. 13)

The gall-bladder was well outlined and showed reasonably normal function. No radiolucent calculi were demonstrated.

Operative Findings.

Theatre. 28.7.58. Mr. Main. Anaesthesia. Dr. Beaton. Thiopentone, Flaxedil, Nitrous Oxide, Oxygen, Fluothane.

A right, epigastric, vertical, rectus-splitting incision was made. The omentum was adherent to the gall-bladder at its neck and fundus, but otherwise the organ was relatively normal in appearance. The adhesions were separated and the common bile-duct exposed. The duct seemed to be normal. It was aspirated and the bile sent for bacteriological examination. Cholecystectomy was then performed and the gall-bladder sent for histological examination. The abdomen was closed in layers and a Penrose drain was left in the liver bed.

Convalescence following operation was uneventful.

Bacteriological Findings.

Culture of common bile-duct bile — No significant organisms isolated.

Pathological Findings.

On macroscopic examination the gall-bladder was found to measure 7 x 2.5 cms. and appeared normal.

On microscopic examination autolysis had occurred but the general architecture was normal. It was thin-walled and the muscle was probably congenitally poor. There was no sign of infection past or present.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at times noted below.

From 10.5.52	to	2.10.53	Sulphaguadidine,	12,506 gms.
From 12.9.57	to	21.9.57	Neomycin,	20 gms.
From 23.12.57	to	2.1.58	Neomycin,	20 gms.
From 31.7.58	to	1.10.58	Achromycin,	9 gms.
From 18.9.58	to	1.10.58	Neomycin,	27 gms.
From 4.10.58	to	11.10.58	Neomycin,	15 gms.

CASE No. 8 PATIENT H.McD.

FIG. 12.

ORAL CHOLECYSTOGRAM:- Little evidence of a functioning gallbladder. No evidence of dye-stuff in bowel. Inconclusive.

FIG. 13. CASE No. 8 PATIENT H.McD.

INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder well outlined. Reasonably normal function. No radio-lucent calculi.

FIG. 13. CASE No. 8 PATIENT H.McD.

INTRA-VENOUS CHOLECYSTOGRAM:- Gallbladder well outlined. Reasonably normal function. No radio-lucent calculi.

RESULTS OF TREATMENT.

This patient was a very occasional faecal excretor of S. paratyphi B. Following courses of oral neomycin in September and December 1957 and cholecystectomy in July 1958 the stool cultures have remained negative until the present time. (7 months from cholecystectomy, 17 months in all).

It is concluded that this patient's virtually dormant carrier state has been eliminated by a combination of neomycin therapy and cholecystectomy.

Note. A post-operative course of neomycin was given in September 1958 to this patient (in common with all other carriers) at a time when stool culture was negative.

CRITERION SUGGESTED FOR VINDICATION OF CONCLUSION.	
Longest recorded excretion-free period before commencement of treatment.	8 MONTHS.
Suggested minimum follow-up period after cessation of treatment. (2-weekly cultures).	24 MONTHS. (until Oct., 1960).

CASE No. 9 (W.F. Male. Present age 58)

This patient was admitted to Hut A.5 from Gogarburn Hospital, Edinburgh on 12th May, 1956, as a S. paratyphi B. carrier. After his admission the patient remained well.

Pre-operative physical examination showed that the tongue was clean and moist and the fauces were clear. Examination of the cardio-vascular system showed that the pulse was regular. The apex beat was found in the fifth inter-space in the mid-clavicular line. The sounds were closed. His blood pressure was 110/75 mms. Hg. Respiratory and central nervous systems showed no abnormality. Abdominal examination revealed no tenderness and there were no abnormal masses.

RESULTS OF PRE-OPERATIVE INVESTIGATIONS.

Liver Function Tests.

Serum Bilirubin	0.2 mgms. per 100 ml.
Thymol turbidity	1 unit.
Serum alkaline phosphatase	6 King & Armstrong units.
Total proteins	8 gms. per 100 ml.
Blood urea	50 mgms. per 100 ml.

Blood Findings.

Blood Group A.B.O. Group A. Rhesus Positive.

Radiological Findings.

Oral cholecystography. (See Fig. 14)

Normally functioning gall-bladder with outlining of the common bile-duct. No radiolucent calculi were demonstrated.

Intra-venous cholecystography.

This examination was therefore not necessary.

Operative Findings.

Theatre. Mr.Main. 7.7.58. Anaesthesia. Dr. Beaton. Thiopentone, Flaxedil, Nitrous Oxide, Oxygen, Fluothane.

A right, epigastric, vertical, rectus-splitting incision was made. The common bile-duct was found to be normal in size. It was aspirated and a specimen of bile sent for bacteriological examination. The gall-bladder was normal in appearance. Cholecystectomy was performed and the organ sent for histological examination. The incision was closed in layers and a Penrose drain left in the liver bed.

Convalescence after operation was uneventful.

Bacteriological Findings.

Culture of common bile-duct bile. No significant organisms isolated.

Pathological Findings.

On macroscopic examination the gall-bladder was found to measure 7.5 c 2.5 cms. It contained normal bile. No stones were present. The wall showed no feature of note.

On microscopic examination a moderate degree of autolysis had occurred prior to fixation. The general pattern, however, was well preserved. The mucosal pattern was complex. The wall showed no sign of inflammatory activity past or present.

Record of Medical Treatment.

The following courses of drugs were given to this patient in quantities and at times noted below.

From	12.5.56	to	28.5.56	Streptomycin, 17 gms.
From	12.9.57	to	21.9.57	Neomycin, 20 gms.
From	23.12.57	to	2.1.58	Neomycin, 20 gms.
From	18.9.58	to	1.10.58	Neomycin, 27 gms.
From	4.10.58	to	11.10.58	Neomycin, 15 gms.

FIG. 14. CASE No. 9 PATIENT W.F.

ORAL CHOLECYSTOGRAM:- Normally functioning gallbladder. Common bile duct visible.

RESULTS OF TREATMENT.

This patient was an occasional faecal excretor of S. paratyphi B. He was admitted from Gogarburn Hospital in May 1956 and detailed records prior to this were not available.

Following courses of oral neomycin in September and December 1957 and cholecystectomy in July 1958 the stool cultures have remained negative until the present time. (7 months from cholecystectomy, 17 months in all)

It is concluded that this patient's virtually dormant carrier state has been eliminated by a combination of neomycin therapy and cholecystectomy.

Note. A post-operative course of neomycin was given in September 1958 to this patient (in common with all other carriers) at a time when stool culture was negative.

CRITERION SUGGESTED FOR VINDICATION OF CONCLUSION.	
Longest recorded excretion-free period before commencement of treatment.	11 MONTHS.
Suggested minimum follow-up period after cessation of treatment. (2-weekly cultures).	24 MONTHS. (until Oct', 1960).

PRECAUTIONS TAKEN TO COMBAT CONTINUANCE OF INFECTION FOLLOWING SURGICAL TREATMENT OF THE ENTERIC CARRIERS.

The patient M.S. had continued to live in the carrier environment after his cholecystectomy and yet his stool cultures were negative. In spite of this, however, it was deemed wise to treat the isolation ward and its patients as a carrier unit. The following precautionary measures were therefore taken upon completion of the surgical treatment:-

WARD.

Kitchen.
Stores.
Bathroom.
Duty-room.

The walls were washed down with carbolic solution, after which they were painted. The floors were carbolized, scrubbed and polished.
The woodwork was washed with carbolic and soda solution and subsequently painted.

SANITARY ANNEXES.

These were fumigated with sulphar candles and then treated in the same way as the Wards. Pre-operative disinfection measures were maintained.

CUTLERY, CROCKERY & UTENSILS.

There were soaked in Deosan for half an hour and then washed in clean soapy water. Deosan was maintained in daily use for cutlery, crockery and food containers generally.

(Even the pet budgerigar's cage was included in the precautionary measures but the budgerigar itself was preserved and only just escaped a dettol bath.)

BEDSTEADS AND FURNITURE.

These were carbolised and polished. Mattresses were fumigated.

BED AND BODY LINEN.

This was carbolised, fumigated and laundered.

SUITS.

The Patients' suits were fumigated and laundered as for bed and body linen.

SHOES, BOOTS, Etc.

These were fumigated.

PATIENTS.

The patients were given dettol baths and clothing which had been fumigated and laundered as noted above.

DURING THE PERIOD OF PRE-OPERATIVE INVESTIGATIONS, OPERATIVE TREATMENT, POST-OPERATIVE CONVALESCENCE AND INDEED UNTIL THE PRESENT TIME, NO CASE OF ENTERIC FEVER, OF PYREXIA OR UNKNOWN ORIGIN OR OF OBSCURE ABDOMINAL COMPLAINT HAS OCCURRED AMONG THE REMAINING HOSPITAL PATIENTS OR STAFF. THE ADVANTAGES OF HAVING ON-THE-SPOT FACILITIES FOR INVESTIGATION AND SURGICAL TREATMENT AND A TRAINED AND ENTHUSIASTIC STAFF ARE THEREFORE COMMENDED.

Note. It is tempting to explain the infrequently positive stool cultures in cases 7,8 and 9 on the basis of cross infection from the more frequently positive carriers but in this connection it is interesting to note that patient M.S. lived among the carriers for over one year after his cholecystectomy without producing a positive stool culture. It therefore seems likely that their biliary tracts were the seat of mild infection in a dormant phase. This is the reason it was decided to treat all patients in the same way, as a single carrier unit.

RECORD OF URINARY EXCRETION OF ENTERIC ORGANISMS BY THE NINE CARRIERS.

PATIENT.	1956.												1957.												1958												1959.											
	JAN.	FEB.	MAR.	APR.	MAY	JUN.	JUL.	AUG.	SEP	OCT.	NOV.	DEC.	JAN.	FEB.	MAR.	APR.	MAY.	JUN.	JUL.	AUG.	SEP.	OCT.	NOV.	DEC.	JAN.	FEB.	MAR.	APR.	MAY	JUN.	JUL.	AUG.	SEP.	OCT.	NOV.	DEC.	JAN.	FEB.	MAR.	APR.	MAY.	JUN.	JUL.	AUG.	SEP.	OCT.	NOV.	DEC.
M.S.	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+									
J.C.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
J.K.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
H.M°M.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
D.S.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
J.Cy.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
W.F.					-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
T.B.	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									
H.M°D.	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-									

\+ POSITIVE URINARY CULTURE.
\- NEGATIVE URINARY CULTURE.

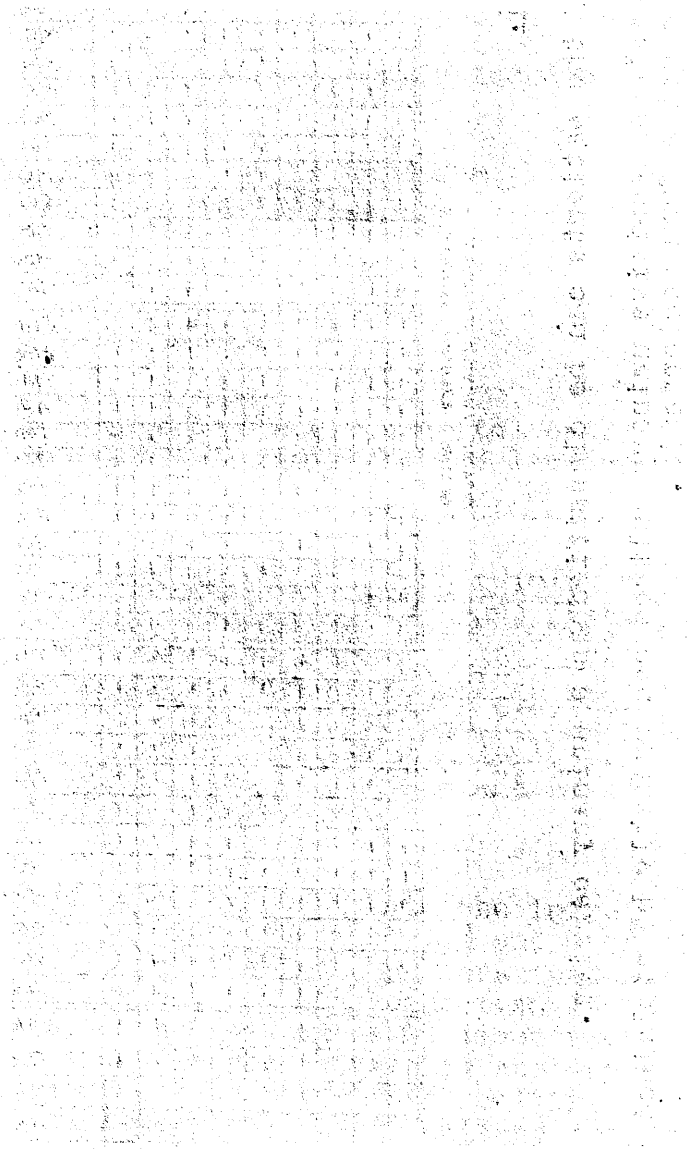
FIG. 15.

CONCLUSIONS.

1. None of the patients can be classified as a urinary carrier.

2. The occasional positive urinary culture can probably be explained as overspill into the urine from bacteraemia.

3. In any event there has been no positive urinary culture since May, 1957.



S E C T I O N 111.

Survey of the literature.

The gall-bladder in enteric fever.

The carrier state in enteric fever.

Surgical treatment in the alimentary carrier. - Analysis.

Treatment by irradiation.

Medical treatment of the alimentary carrier. - Analysis.

SURVEY OF THE LITERATURE.

THE GALL-BLADDER IN ENTERIC FEVER.

Ledingham and Arkwright (1912), Gay (1918), Browning, C.H. et al. (1933) and Topley and Wilson (1946) give excellent reviews of the early work carried out on this subject.

At Post-Mortem examination in a case of enteric fever there are four situations ouside the intestines where enteric organisms are constantly present - spleen, enlarged mesenteric glands, bone marrow and gall-bladder. Von Futterer (1888) was apparently the first to show that S. typhi could be isolated from the gall-bladder in fatal cases of the disease. This was confirmed by Gilbert and Girode in 1980. In 1891 Blachstein and Welch had recorded that S. typhi when injected intra-venously in rabbits soon established itself in the gall-bladder and might still be present for as long as 128 days after inoculation. Pratt in 1901 isolated S. typhi from the gall-bladder in twenty-one of thirty fatal cases of typhoid fever and Scott in 1915 isolated it in twenty-four of twenty-eight cases. Findlay and Buchanan, (Glasgow 1906) isolated organisms from the gall-bladder twenty-five years after an attack of typhoid fever and at the same time demonstrated them in the faeces. In some cases e.g. Dudgeon (1908) S. typhi had been isolated from the gall-bladder in cholelithiasis where there was no history of typhoid fever. (Ledingham & Arkwright 1912, Gay 1918). Richardson (1899) recorded observations similar to those of Blachstein in rabbit experimentation and noted that some of the rabbits developed gall-stones. (This seems to be of significance in relation to later discussions between Whipple and Mathews in 1929 as to whether the presence of gall-stones in the gall-bladder of carriers were causal of the persistence of the carrier state or resulted from it. It also bears a relation to the finding in the present series of gall-stones in the most persistently positive carriers.) This work was also confirmed by Gay in 1918. Aird in 1949 stated that a patient with no signs of cholecystitis during the fever may develop gall-stones years later and sometimes the typhoid bacillus may be cultured from these.

ROUTE OF INFECTION.

Topley and Wilson (1946) take it as the generally accepted view that the bacilli reach the gall-bladder from the blood by travelling from the liver capillaries to the bile canaliculi and thence along the bile ducts. (See Doerr 1905, Lemiere and Abrami 1907, Nichols 1916, Gay 1918.) Illingworth & Dick (1943) in discussing the possible routes by which organisms may reach the gall-bladder in excretors, favour the view that they reach the liver via the portal blood stream and then escape into the bile and so reach the gall-bladder. (See discussion on histological findings page (162) 209). They say it is known that in typhoid fever, in many infections in the portal area and even in constipation organisms find their way into the bile and that there is therefore strong prima facie evidence for this view. Aird (1949) states that of the five possible routes of infection of the gall-bladder - ascent along the common bile-duct from the duodenum, lymphatic infection from the duodenum, lymphatic spread from an infected liver, haematogenous infection, infection of the gall-bladder by organisms which have passed in the portal blood to the liver and have been excreted in the bile, the last is probably responsible for typhoid cholecystitis.

CARRIER STATE IN ENTERIC FEVER.

In 1902 Robert Koch drew attention to the typhoid patient or convalescent as the most serious source of the spread of the disease.

In 1933 Browning, Coulthard, Cruickshanks, Guthrie and Smith in a masterly publication in the Special Reports Series of the Medical Research Council, gathered all the known information regarding chronic enteric carriers and their treatment up to that time. The following facts have been taken from their memorandum.

1. There is overwhelming evidence that human beings constitute the sole source of the specific bacteria and that chronic "carriers" form an important part of this supply of infection, a carrier being one who has within himself the causative organism of an infectious disease but who shows no other signs of that malady.

2. With regard to the duration of the carrier state the following statements are generally accepted.

   a) In convalescence from enteric fever a considerable number of persons excrete the specific organisms for short periods - "Temporary carriers."

   b) The majority of those who continue to excrete enteric bacilli for six months after the acute attack will continue to do so.

   c) Those who continue to excrete the bacilli after a year will not become cured spontaneously and are to be regarded as permanent ("chronic") carriers.

3. A faecal excretor of enteric organisms may belong to one of two types - the biliary carrier who may harbour an organism in the gall-bladder or liver and bile-ducts or both, and the true intestinal carrier in whom bile is not infected, the organisms persisting in the intestinal tract.

   * "While the existence of the latter type of carriers seems to have been established by various observers it is certainly rare."

4. With regard to biliary carriers the experimental evidence suggests that a definite lesion of the gall-bladder wall is chiefly responsible for the carrier state.

5. The gall-bladder may show little histological evidence and gall-stones may be absent even when the evidence points to the gall-bladder being the site of infection.

6. The infection may persist in the ducts (e.g. they quote a case of a female patient who had congenital absence of the gall-bladder.)

7. Typhoid bacilli may persist in extra-hepatic and extra-biliary situations e.g. in the bone marrow.

8. There are four or five female to one male carriers.

9. No conclusion can be drawn from the culture of the gall-stones since the organisms readily penetrate cracks in the stones.

10. Histological changes in the gall-bladder in biliary and enteric carriers:-

The organ may show little abnormality. Gall-stones are not common. The lining epithelium may show very little evidence of catarrh even in the presence of gall-stones or there may be some desquamation in places. The most marked change which has been observed in the gall-bladder, however, consists in localised and diffuse collections of cells in the mucosa which are mainly plasma cells andlymphocytes with scanty eosinophils. At places, the cellular foci closely resemble hyperplastic lymphoid nodules with germ centres. There is no definite evidence as to the presence of the bacilli in the substance of the mucous membrane. The other coats appear normal. Indeed there is considerable support for Garbat's view that in such cases the carrier state is maintained by the gall-bladder acting as a "test tube containing the bile medium in which typhoid bacteria propagate without affecting the gall-bladder itself."

11. Mixed typhoid and paratyphoid carriers occasionally occur.

12. Bacilli may occasionally occur in the urine in chronic intestinal carriers.

13. The modes of spread of infection by carriers are given as:-

    a) Contamination of foodstuffs especially milk.

b) Pollution to water supply.

c) Soiled linen.

d) Personal contact.

In discussing the control of infection due to carriers, Browning et al. state. "As compared with the carrier who is sane, the control of the enteric carrier in mental asylums is even more difficult. Such persons are continual menaces both to inmates and attendants, and often are the cause of repeated outbreaks of the infection. (See page 6). In Scotland all known lunatic carriers have recently been segregated in a single institution. (15th Annual report of general Board of Control, Edinburgh 1929). (See page247). In view of the good results which have been shown to follow operative treatment of chronic intestinal excretors it was suggested that carriers in Scottish Asylums be subjected to operation. However, the General Board of Control held that the carrier state does not constitute illness and that any surgical interference would not be for the benefit of the carriers, but solely for the good of the community; therefore the authority concerned may be liable to penalty should the carrier regain sanity and bring an action for wrongful treatment. As has been pointed out above, however, there is clear evidence that the carriers as a rule are not healthy persons." (See M. S. case No. 1 page6) "and that in suitable cases operative treatment directed towards the gall-bladder or urinary tract, which is the only hopeful therapeutic procedure, would benefit the individual as well as the community."

SURGICAL TREATMENT IN THE ALIMENTARY ENTERIC CARRIER.

In 1907 Dehler reported the treatment of two carriers by cholecystostomy. One was cured and one remained a carrier.

In 1908 Grimme described the cure of a patient by cholecystectomy.

Thereafter reports of single cases and series operated upon occurred in the literature. The procedures recommended were:-

1. Cholecystostomy.
2. Cholecystectomy.
3. Cholecystectomy and drainage of the common bile-duct.

It is interesting to note here that pioneering work in this field was carried out in the Surgical Wards of the Western Infirmary in Glasgow. Dr. John Park, Medical Superintendent of Falkirk & District Royal Infirmary recalls with relish and enthusiasm the excitement of those days in 1923/24 when, as house-surgeon to Mr. Farquhar Macrae he was intimately concerned with three enteric carriers who were operated upon at that time. Cholecystostomy was not thought to be a sufficiently radical procedure and cholecystectomy was presumably not always easily possible (mainly due to difficulties with anaesthesia.) Mr. Macrae, however, suggested the use of the operation of cholecyst-gastrostomy and carried out this operation on two patients. Its aim was to establish drainage of bile into the stomach and at the same time allow access of the gastric content into the gall-bladder, since it had previously been shown that typhoid and para-typhoid organisms were rapidly killed in human gastric juice. One of the two patients was pronounced cured but the other was not and was subsequently submitted to cholecystectomy. A third carrier had a cholecystectomy as the chosen operation. The details of the three cases are worth recording. The relevant journals were unearthed from the archives of the Western Infirmary. Supplemental details have been taken from Browning et al.

1. K.1. (faecal excretor of S. typhi). A female aet. 27 had typhoid fever in 1914. In 1915 she became a kitchen-

maid at a farm and six months later one of the man-servants contracted typhoid fever. She then left the farm to keep house for her two brothers. One brother developed severe typhoid fever in 1919. On 4th May, 1923 cholecyst-gastrostomy was performed, the anastomosis measuring ½". The common bile-duct was not ligated. The gall-bladder was found to be thickened and its neck was adherent to the liver. No stones were found. Culture of the bile was positive. On histological examination the gall-bladder showed congestion and diffuse inflammatory change in the substance of the wall. Plasma cells, lymphocytes and a few eosinophils were found in the sub-mucosa. A few polymorphs were noted, some between the columnar cells.

Some smaller lymph foci resembled hyperplastic nodular lymphoid tissue with a germ centre. In the deeper layers inflammatory changes were very slight. Four weeks after operation the stools were negative and remained so for over five years.

2. H.T. (chronic faecal excretor of S. typhi and S. Paratyphi B.)

A female patient aet. 53 developed enteric fever in 1913 and was nursed at home. Shortly afterwards her brother, whose house she kept, took typhoid fever and died. Two further cases in 1914 were attributed to her. In 1915 she became housekeeper to a family and the householder and another man who took his meals in the house both contracted typhoid. A further case occurred in the house later in 1915. Next the cook on the farm where H.T. milked the cows took typhoid. In May 1916 she went to live by herself and two cases occurred in a neighbouring family. On 4th May, 1923 cholecystectomy was performed and the "hepatic duct" was drained for twenty-seven days. Eight weeks after the operation the stools became negative and remained negative until her death from intercurrent disease nineteen and a half months later. The gall-bladder was found to be enlarged and distended but looked otherwise normal. The mucosa was thickened and honeycombed and the plicae were exaggerated. Thirteen facetted stones were present. Culture of the bile was positive. On histological examination congestion was noted and there were foci of leucocytes in the sub-mucosa, in the centre and the base of the plicae often near small blood vessels, with a more diffuse cellular change in the other parts. The cells were mainly plasma cells and lymphocytes with a few eosinophils. Again a few polymorphs were noted between the columnar cells.

Some of the foci resembled hyperplastic nodular lymphoid tissue with a so-called germ centre. A less marked degree of inflammatory change was found in the other layers.

3. M.D. (A chronic faecal excretor of S. Paratyphi B.)

A female patient aet. 39 was treated in hospital for enteric fever from December, 1918 to February, 1919. In May 1920 she became a farm-servant and in July two other servants took "flu" and "rheumatic fever" respectively. In December 1920 a lad who had just come to the farm took enteric fever. On 17th July, 1923, a cholecyst-gastrostomy was performed. The common bile-duct was not ligated. No stones were found. The gall-bladder was small but looked normal. Culture of the bile was positive. The histological changes were as before. Although the changes tended to be diffuse a focal arrangement was again seen. After operation the faeces continued to yield the specific organisms and cholecystectomy was carried out on 19th July, 1924. On this occasion the gall-bladder was found to be distended. The anastomotic opening was minute and Mr. Macrae was of the opinion that, had the original opening been bigger, the result would have been more satisfactory since there was obviously no drainage. The gall-bladder was removed and the "hepatic duct" drained for twenty-five days. For fourteen months following this operation S. Paratyphi B. was isolated from the stools on several occasions but thereafter the stools were negative for a period of three years.

In 1925 Vosburg and Perkins practised appendicectomy with cholecystectomy for the carrier state on the grounds that the lymphoid tissue of the ducts was infected during an acute attack and the organism might therefore persist and multiply in this situation.

In 1927 Haaland & Haaland reported the treatment of fourteen carriers. (Five typhoid and nine paratyphoid B.) claiming 84.5% of cures. One patient died six days after operation and one developed a permanent biliary fistula. All but one had stones. Eleven were cured. The criteria in this paper are good. All cases had been carriers for over one year and all had negative tests for over three

months post-operatively. Their note on the histological findings is not detailed but they record acute-on-chronic cholecystitis in two cases, chronic cholecystitis in seven, acute cholecystitis in one and normal histology in four.

In 1929, an interesting paper was published by Whipple who stated that the lack of a more positive stand for surgery in dealing with these unfortunate individuals was generally due to two factors.

1. Some carriers after cholecystectomy or cholecystostomy continued to be carriers.

2. The operations were possibly carried out by incompetent surgeons in Asylums or State Institutions with a high mortality so that prejudice arose against surgery.

He quoted a report of the New York State Department of Health (1929) which summarised the results of gall-bladder operations for typhoid carriers in New York State excluding New York City.

14 known carriers were considered cured by operative treatment.

2 were probably cured.

5 were not cured.

5 died after operation.

Whipple's paper reports 14 cases at the Presbyterian Hospital. - 13 carriers of S. typhi and 1 carrier of S. Paratyphi B.

Of the 8 patients who were known carriers before operation 6 were cured, 2 were not.

Of the 6 patients who were not known carriers before operation, 3 were cured and 3 were not.

2 patients had cholecystostomy and 12 had cholecystectomy. Two of the twelve died. Both had cholangitis and pancreatitis at operation.

The results of Whipple's series are open to some doubt because six cases were operated upon during "late" convalescence. The remaining eight were known carriers for six months to two years only. Post-operative follow-up was inadequate by accepted modern standards.

Whipple makes the following interesting comments:-

1. "The presence of a gall-stone, porous and pervious to typhoid bacilli prevents the gall-bladder from freeing itself of infection for it both hinders mechanically the emptying of the gall-bladder and re-infects the fresh incoming bile."

2. "Cholecystectomy gives a 70% chance of cure."

3. "In as much as the great majority of bile carriers have gall-stones and chronic cholecystitis the operation is not necessarily pro bono publico but may be looked upon as of benefit to the individual as well as to the community."

In 1930, Eichhoff (quoted by Littman et al.) reviewed the European literature and collected 102 cases in which gall-bladder surgery had been employed in treatment. He chose six months as a minimum follow-up period. 84% of ninety-four cases were cured by operation.

In 1932, Holst reported the treatment of twelve carriers; two of S. typhi and 9 S. Paratyphi B. Eleven patients had cholecystectomies and one had cholecystostomy. Two patients died, one on the first post-operative day and one five days after operation, (both of cardiac failure).

Post-operative follow-up was inadequate by accepted modern standards.

Nine cases were discharged negative, one being persistently positive.

Holst makes the interesting statement that, "While in the surgical department the carriers just mentioned may be assumed a few times to have been the source of fresh typhoid cases arising in the Wards in spite of precautions."

In 1933 Bigelow and Anderson reported twelve cases of their own cured by cholecystectomy. Of those, nine were operated upon to cure the carrier state. Threewere operated upon for symptoms. All had stones.

In the paper there is no note of pre-operative stool culture frequency and no note of operative findings or histology. Five cases showed positive cultures during convalescence. They recommend follow-up by monthly stool cultures for one year and make the comment that the operation was considered beneficial to the patient's well-being.

They also report Vogelsang and Haaland in 1931 as bringing the Haalands' series up to date, giving a total of 25 cases of whibh 19 were said to be cured by cholecystectomy.

In 1933, Browning et al. reviewed the results of operation and selected only those cases which satisfied their criteria (i.e. convalescent carriers excluded and follow-up period was considered to be adequate.) From their figures there was no support for the view that carriers of paratyphoid organisms were less amenable to surgical treatment than carriers of S. typhi.

In fifty-seven cases forty-three were cured (75%). Seven of ten cholecystostomies were said to be cured.

In 1933, Senftner and Coughlin recorded 68% of cures in sixty-eight operated cases. Their method of analysing the figures however was complicated and presupposed the necessity for making pre-operative duodenal cultures. The mortality rate for all cases was 14.7%. Of those submitting to operation primarily for the cure of the carrier state only 7.1% died from operative treatment.

In 1935, Hanssen reported five cases who had been carriers for periods of from three months to three years. Bile and stool cultures were positive. One patient was operated upon three months after an acute attack and should be discarded. (Author). Cholecystectomy was carried out in five cases and gall-stones were found in four. S. typhi was cultured from the gall-bladder wall and its contents in all cases and from stones and cystic gland in two cases.

All cases were said to have been cured but the follow-up is inadequate by accepted modern standards.

Hanssen quoted Berglas as giving a figure of 75% of cures from operative treatment.

In 1936, a report was published by the Infectious Disease Sub-Committee of the R.M.P.A. A questionaire was sent to the Medical Superintendents of sixty-four hospitals asking for a report on all cases of cholecystectomy carried out on enteric carriers.

SUMMARY OF FINDINGS.

1. Successful results followed operation in 77% of cases.

2. Mortality from operative treatment was 21%

3. Survival with continuance of infectivity occurred in 2%.

4. Age in itself did not appear to be related to mortality.

5. The presence or absence of depraved habits did not appear to be of marked importance.

6. After operation the excretion of bacilli usually ceased within three weeks but might continue up to about one year.

They made the following recommendations.

1. Cholecystectomy appears to be the only treatment which has any reasonable chance of success in faecal excretors of the typhoid group of organisms.

2. Before operation it must be ascertained that the patient is not a urinary carrier in which case cholecystectomy is useless.

3. Before operation, bacteriological tests must be made for not less than oneyear.

4. As long as the patient is reasonably fit age alone is not a contra-indication to operation.

5. With cholecystectomy one must expect about 75% of cures.

6. The operative mortality appears to be about 20%.

7. The chance of operation failing to cure the carrier condition is small - about 2 to 5%.

8. There is evidence that curing the carrier condition is beneficial to the health of the patient.

9. After operation cases should be tested bacteriologically at weekly intervals or more often for at least a year in order to make sure that they are non-infective before being returned to the general wards.

In 1936, Lobsenz recorded a single case, a female aged 56 who had been a carrier of typhoid organisms for one year after an acute attack. During the year, she had had two X-ray and 20 short-wave treatments over the gall-bladder. (She had one attack of cholecystitis lasting only 24 hours.)

Cholecystectomy and appendicectomy were performed. Examination of the gall-bladder showed the mucosa and the sub-mucosa to be packed with round cells, proliferative stromal cells and plasma cells, with occasional polymorphs. In the sub-mucosa numerous lymph follicles were found eith a dark outer zone and pale central area showing reticulum-cell hyperplasia. Round-and plasma-cell infiltration of the interstices of the muscularis was noted. There was fibrosis of the serosa. The findings were those of diffuse, sub-acute cholecystitis. The appendix was the seat of chronic fibrosing obstructive disease. Cultures of the bile, gall-bladder and ducts were negative. Seven negative post-operative stools were recorded.

In 1936, Buyze reported a typhoid carrier cured by cholecystectomy.

In 1937, Coller & Forsbeck in an interesting paper

pointed out that the benefits of cholecystectomy are:-

1. The occasional case that occurs even after a person knows himself to be a typhoid carrier is prevented.

2. The former food-handling carrier is able to resume his occupation.

3. The mental depression frequently observed in carriers is relieved.

4. Potential or actual gall-bladder disease is eradicated.

5. The health department is released from the expense of controlling a potential source of infection.

They stated that the literature was not clear concerning the mortality rate from cholecystectomy in carriers since it was not always stated whether the carrier was submitted to operation mainly to cure his carrier condition or because of the urgency of his clinical symptoms. "To deprecate surgical intervention for the cure of the carrier state because of deaths occurring among carriers operated upon because they were seriously ill with gall-bladder disease is obviously illogical."

They report eighteen cases (with excellent pre- and post-operative criteria.) 67% had slight to marked symptoms of gall-bladder disease. Two were operated upon primarily for the relief of symptoms. No deaths occurred.

In 1937, Lynn, in a review, stated that the typhoid problem was that of an endemic disease. It had long since ceased to be an epidemic one.

In the city of Baltimore in 1937 he estimated that there were approximately 158 carriers and to these a total of 627 cases of typhoid fever could be attributed.

A housewife who had had typhoid fever was found to be a carrier eighteen years later and 106 cases of typhoid fever were traced to her! Lynn believed that the operation of cholecystectomy had proved to be the most efficient operation until that time. He stated that, "In reviewing the results obtained by the various writers

on this subject one is struck by the uniformity of success, all recording 80 to 85% cures of the individuals submitting to operation."

In 1941, Badia reported a chronic typhoid carrier treated by cholecystectomy. A large, distended gall-bladder was found containing a single calculus. The histological findings were those of chronic, suppurative cholecystitis. Culture of the gall-bladder contents was positive. After operation the patient developed typhoid septicaemia and obstructive jaundice and died on the 13th day.

Badia felt that in this case he should have carried out preliminary cholecystostomy and later cholecystectomy. His paper includes a review in which the following points were made.

1. Patients over 45 years of age with a long history are poor surgical risks.

2. The longer the duration the greater is the possibility that the infection has progressed from the gall-bladder into the ducts and liver.

3. The finding of negative bile specimens in a carrier is a contra-indication to cholecystectomy.

4. There is no justification for subjecting a patient to cholecystectomy without knowing that he is a chronic bile carrier unless there is definite evidence of gall-bladder pathology.

5. The Widal Test may be negative. To carriers who have not had typhoid fever and who have a negative Widal, typhoid vaccine might be given before operation. (His case developed a positive Widal after operation.)

6. 5% Glucose should be given as a clysis or intra-venously before and after operation.

7. Bleeding, clotting, and prothrombin-time should be ascertained.

In 1941, Vogelsang reported twenty-three new chronic S. paratyphi B. carriers in Western Norway. All were "intestinal". Seventeen old chronic carriers were found

in endemic foci. Six new cases were found by control of convalescents where excretion of bacilli had persisted.

In 12 cholecystectomy was carried out.

In 3 no benefit was obtained from operation.
In 2 the bacteriological control was not complete.
In 8 the operation was successful, in that the stools became negative.

In 1942, Coller et al. reported 18 cases, 16 of whom were cured by cholecystectomy (88.9%). An additional three were apparently cured.

They stated that 15% of carriers had negative stool cultures and that one post-operative duodenal culture was considered to be necessary. An interesting point in this paper is that five carriers produced positive stools for from 102 to 167 days following surgery. One carrier continued positive for 308 days.

In 1942, Crabstree added 21 cases to Coller's group and found 88.9% of cures. (Quoted by Littman et al. 1949).

In 1943 Honig reported a typhoid carrier who had a cholecystectomy performed and whose stools did not clear for 18 months. He attributed Littman's success to persistent post-operative therapy --- antispasmodics, sedatives, hydrochloric acid (she had achlorhydria) and frequent feedings.

He comments, "The hopeless attitude which condemns a persistent typhoid carrier following cholecystectomy as an eternal carrier should be revised."

In 1945, Pheemster and Smith reviewed the situation regarding cholecystectomy in enteric carriers in Massachusetts. Of sixty-eight carriers, sixty-three were cured, five were not. (92.6%). They also recorded four failures with sulphaguanidine and sulphathiazole.

In 1947, Stone et al. described a carrier treated by cholecystectomy. The stools remained positive for three weeks. After a course of penicillin and sulphamerazine they became and remained negative.

In 1949, Littman et al. reported thirteen carriers treated by cholecystectomy. They lived together sharing the same dining-room and kitchen. The duration of the carrier state averaged twenty-seven months before operation. Following cholecystectomy they lived among many other carriers and twelve remained cured. They were studied for five years after surgery.

In 1949, Aird stated that if typhoid bacilli were not isolated from the removed gall-bladder the subject of operation was likely to remain a typhoid carrier and that even when active cholecystitis was demonstrated in the removed organ there was no guarantee that infectivity would cease.

In 1950 Pearson and Wolfe, in a review, stated that in the State of Washington the number of reported carriers in 1947 was thirty-eight and in 1948, forty-four. The number of cases of acute typhoid fever in 1939 was 263. In 1948 there were 12.

They stated that "Increasing recognition of the carrier state may well be the decisive factor in the declining incidence of the acute disease but its eradication depends upon successful treatment of the carrier."

They reported a carrier treated by chloromycetin, 0.5 gms. and 0.25 gms. two hourly for eight days. This produced no effect on the stool cultures. They then tried the effect of long-acting penicillin and sulphadiazine, 1 gm. four hourly for seven days. The stools became negative for two days only during treatment. Cholecystectomy was then performed (chronic cholecystitis and one stone being found). The stools became negative in five months and remained negative for one year. Their conclusion was that cholecystectomy remained the best method of therapy for the typhoid carrier state

In 1952, Acton et al. reported a typhoid carrier of six years duration cured by the combination of cholecystectomy and 92 gms. of chloramphenicol.

In 1955, Hiddlestone and Murphy reported failure from chloromycetin therapy and cure by cholecystectomy in the same patient but the follow-up reported was inadequate. Culture of the gall-bladder was positive. It seemed normal but contained one stone.

In 1957 Lemmon et al. reported the treatment of four mental patients in a state hospital who were all cured by cholecystectomy.

In one, a course of chloromycetin failed to cure. At cholecystectomy chronic catarrhal cholecystitis with fibrosis and cholelithiasis was found. A positive culture was obtained from the gall-bladder wall.

In the second, cholecystitis and stones were found.

In the third, no stones were found and culture of the gall-bladder grew a para-colon bacillus.

Their conclusion was that, to date, there was no effective non-surgical treatment for the carrier state. Chloromycetin was said to be the drug of choice in acute typhoid fever but such was not the case in dealing with the chronic typhoid carrier state.

Note. There has been a good deal of controversy in the literature regarding duodenal intubation and the value of bile cultures obtained in this way.

Lemmon et al. state, "A negative duodenal intubation with a positive faecal culture does not rule out biliary tract infection."

In 1957, Flynn reviewed the situation in Ireland. He stated that the previous decade had seen a progressive fall in the number of cases of typhoid fever occurring annually in Ireland. Despite this favourable trend, however, enteric fever was still a disease of major Public Health importance and notification of paratyphoid B. fever showed little or no tendency to fall.

He estimated that there were, at that time, approximately 285 chronic enteric carriers in Ireland. Five of six treated by cholecystectomy were cured. One died two days after operation of acute heart failure. He states that, "The gall-bladder is the sole site of persistence of infection in the vast majority of chronic faecal carriers. Pure intestinal carriers probably do not exist. It is likely that infection may persist in the upper bile passages in a few cases.

Flynn also felt that it was unlikely that gall-baldder wall infection played any part in the multiplication of bacilli.

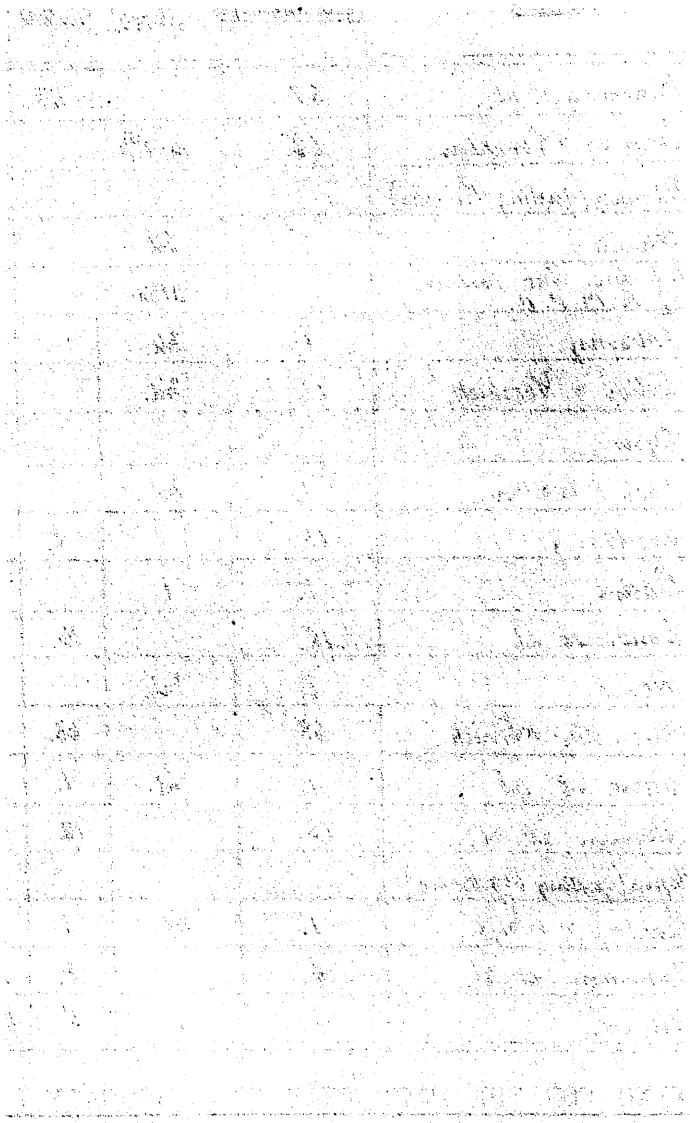
CHOLECYSTECTOMY IN THE TREATMENT OF ENTERIC CARRIERS.

The following table has been extracted from the literature. It indicates the results given by various authors.

FIG. 16.

YEAR.	AUTHOR	Nº OF CHOLECYSTECTOMIES	MORTALITY (IF STATED).	Nº CURED	% CURED	REMARKS.
1933.	Browning et al.	57.		43.	75%	A. Review.
1933.	Senftner & Coughlin.	68.	14·7%.		68%	A. Review.
1935.	Hanssen (quoting Douglas).				75%	
1935.	Hanssen.	5.	Nil		100%	
1936.	Inf. Dis. Sub-comm. of R.M.P.A.		21%		44%	A. Review.
1936.	Lobsenz.	1.	Nil.			
1934	Coller & Vorsbeck.	18.	Nil.		100%	
1937.	Lynn.				80-85%	A. Quotation.
1941.	Levi & Willen.	1.	Nil.			
1941.	Vogelsang.	13.		8.		
1941.	Badia.	1.	1.			
1942.	Coller et al.	18.		16.	88·9%	
1943.	Honig.	1.	Nil.			
1945.	Phemister & Smith.	68.		63.	92·6%	A. Review
1947.	Stout et. al.	1.	Nil.	1.		
1949.	Littman et al.	13.		12	92·3%	
1950.	Flynn (quoting Vogelsang).				80%	
1950.	Pearson & Wolffe.	1.	Nil.	1		
1957.	Lemmon et al.	4.		4.	100%	
1957.	Flynn.	6.	1	5.	83·3%	

ALLOWING FOR THE FACT THAT THE ADEQUACY OF THE CRITERIA AS REGARDS PRE-OPERATIVE DURATION OF CARRIER STATE AND PERIOD OF POST-OPERATIVE OBSERVATION CANNOT BE REGARDED AS ACCEPTABLE IN ALL CASES, THE CURE RATE FROM SURGICAL TREATMENT APPEARS TO BE IN THE REGION OF 85%.



TREATMENT OF ENTERIC CARRIERS BY IRRADIATION OF THE GALLBLADDER.

In 1935 Gulbrandsen report four carriers of a group of twelve successfully treated by X-ray therapy.

In 1937 Ebson et al. stated that irradiation of the gall-bladder in twelve typhoid carriers failed to destroy the organisms. Culture of the bile and faeces were persistently positive. The method was also ineffective in one urinary carrier treated. Surgical removal of the gall-bladder in two cases led to cure.

MEDICAL TREATMENT OF ALIMENTARY ENTERIC CARRIERS.

In 1933 Browning et al. reviewed the various medical measures which had been given a trial up to the year 1933. These measures included:-

Drugs. Intestinal antiseptics with or without charcoal or coal dust, mercurochrome, oral acriflavine, phenolic derivaties, bismuth salicylate, sodium salicylate, salol, acid sodium phosphate, napthalene, acetazone, felamine, yadil, baptisa, vinegar, raw onions, sodium bicarbonate, sodium tetra-iodophenolphthalein plus X-rays, kaolin, dried ox bile and other chòlagogues.

Physiotherapy. Non-surgical biliary drainage (Lyon.)

Alterations of the flora and re-action of the intestine.

Sour milk therapy, sodium acid sulphate, intestinal implantation of antagonistic coliform bacilli.

Typhoid bacteriophage.

Vaccine therapy.

These methods were uniformally unsuccessful.

TREATMENT WITH IODOPHTHALEIN.

In 1941 Enright reported the apparent cure of a typhoid carrier with soluble iodophthalein.

In 1942 Saphir et al. reported the treatment of sixty-five biliary carriers with soluble iodophthalein. The stool was freed of organisms in 7.5%.

After the introduction of specific chemotherapy in the form of sulphonamide drugs, manypapers appeared, giving the results of treatment by these compounds in enteric carriers. This opened up a new era of hope that a drug might be found which would eliminate the last strong-hold of this persistent disease.

TREATMENT WITH SULPHONAMIDES.

In 1941 Levi and Willen treated a carrier, in whom cholecystectomy had failed, with sulphaguanidine. Ten faecal specimens were subsequently negative.

In 1942 Saphir et al. reported the treatment of five carriers with sulphaguanidine. The drug had no effect on bacillary excretion in the stool.

In 1942 Cutting & Robson reported the treatment of 6 typhoid carriers with thionol, phenothiazine, soluble iodophthalein, sulphaguanidine and sulphadiazine. Their conclusion is as follows:-

"As yet there is no dependable or efficient drug for typhoid carriers though further chemotherapeutic development might be attempted with the sulphaguanidine type of compound."

In 1942 Kirby & Rantz reported that succinyl sulphathiazole produced a decided alteration in the physical characteristics of the stools but typhoid bacilli remained viable in the stools of three carriers during two weeks of therapy with the drug.

In 1942 Hoagland reported the treatment of two carriers with sulphaguanidine (20 grams per day for six days). In one, he claimed success, the stools remaining negative for 43 days. In the other the stools were negative for seventeen days only. This follow-up is unacceptable by modern standards.

In 1942 Watt and Peterson reported the treatment of three typhoid carriers with sulphaguanidine (15 grams per day for 14 days). They concluded that sulphaguanidine in the dosage used was not effective in the treatment of cases of typhoid fever or carriers of S. typhi.

In 1943 Burroughs and Freyhan treated a single carrier with sulphaguanidine, (6 to 18 grams per day, with a total dosage of 174 grams) without effect.

In 1947 Nelson reviewed the treatment of nine carriers (who appear to have been mainly urinary in type) and claimed cure in seven from treatment with tartar emetic, N.A.B. and M & B. 693. This investigation does not seem to be directly relevant to the present series.

TREATMENT WITH PENICILLIN AND SULPHONAMIDES.

New hope arose with the discovery of the antibiotics.

In 1946 Professor Bigger of Dublin produced important experimental evidence demonstrating a syngergistic action between penicillin and sulphathiazole. Using broth freed from sulphonamide-antagonising substances, he found that sulphathiazole had an inhibiting effect on the growth of S. typhi in vitro and that it had some bactericidal effect, but only on a small inoculum.

Penicillin in concentrations up to 8 units per c.c. reduced, but did not prevent, the growth of S. typhi in broth.

The combination of penicillin and sulphathiazole, however, had a pronounced bactericidal effect on S. typhi. He suggested, on the basis of his experiments, the trial in enteric carriers, of sulphathiazole in full doses with penicillin, 2½ to 3 million units per day for 7 days. If, on subsequent observation, there was still evidence of

typhoid organisms in the stool, this treatment should be continued for a further four days.

In 1946 Commerford et al. treated two typhoid carriers (one of whom continued to excrete S. typhi after cholecystectomy) with penicillin and sulpha-thiazole on the lines suggested by Bigger, and obtained encouraging results. The stools remained negative for 130 to 116 days, respectively, though the validity of this criterion is open to criticism. (Author). There was, however, a drop in the Vi antigen titre which is regarded as significant of cure by Topley & Wilson. Comerford et al. suggested the application of this method to a large number of carriers.

In 1946, Riser et al. treated a typhoid carrier with 2,350,000 units of penicillin over a seven-day period. He showed negative rectal cultures for five months. (The patient had been presumed to have had typhoid fever 19 years previously and was a foodhandler discovered on routine check). No cases had ever been traced to him. Sulphadiazine (35 grams in 5 days) apparently had no effect.

A second carrier similarly treated "made only a temporary response."

In 1947 Bersohn & Nelson described the treatment of a urinary carrier with penicillin and sulphathiazole. (The patient worked on a dairy farm; the duration of his carrier state was not known). He was discovered by routine serological tests. The urine after treatment remained free of typhoid bacilli for four months.

In 1948 Fry et al. reported the treatment of seventeen typhoid carriers with massive doses of penicillin and moderate doses of sulphathiazole with apparent cure in only three cases.

In 1949 Bigger and Daly reported that they had, until then, treated ten carriers with sulphathiazole (52 grams) and penicillin (30 mega units) over 6½ days.

One patient died of intercurrent disease 40 days afterwards.
One was cured.
Eight of the ten relapsed in 5 to 56 days.
Three patients were re-treated by an intermittent method - two were said to have been cured.

Bigger and Daly claimed the method to be superior to any previously adequately tested.

In 1949, Rumball & Moore, in their paper, stated that infection of the gall-bladder was one of the most important features of the carrier state but that cholecystectomy was not uniformly successful. They stated that the gall-bladder was not the only focus in the alimentary tract where chronic infection could reside for many years. They reported a case treated with two separate courses of penicillin and sulphamerazine.

In the first case, a low dosage of sulphamezathine was given and the result was unsuccessful.

In the second, a high dosage of sulphamerazine was given and the outcome was successful.

Their criterion of cure was the finding of weekly negative stool cultures for nine months with the disappearance of Vi. antigen.

In 1950, Moore and Rumball reported the treatment of a second case by high dosage of penicillin and sulphamerazine in which chloramphenicol therapy had been unsuccessful. A nine months' cure was obtained.

In 1951, Douglas & Hubbard reported three carriers treated with penicillin and sulphamerazine with a sulphonamide blood level above 10 mgms. per 100 ml. In two cases the treatment was unsuccessful.

TREATMENT WITH ANTIBIOTICS.

In 1941, Abraham et al. stated that penicillin was ineffective in the treatment of typhoid fever and other infections with gram negative bacilli.

STREPTOMYCIN.

In 1945, Rutstein et al. held a hope of new possibilities in the treatment of enteric carriers by the introduction of streptomycin. They studied the

absorption and excretion of streptomycin in four typhoid carriers. (The drug was given three-hourly in doses of 75,000 and 150,000 units intramuscularly with 31,250 units orally). The blood level at 150,000 units three-hourly rose to 5 to 20 units per ml. Certain toxic manifestations unique for this drug were noted. (Therefore the dose was adequate.- Author). No significant bacteriostatic effect on S. typhi in the stool was obtained with intra-muscular infection but with three-hourly oral administration a definite transitory bacteriostatic effect was obtained on the organisms in the stool in two of the three patients treated.

In 1947, Pulaski and Amspacker showed that, in vitro, 87% of cultures of gram negative bacilli were inhibited by 16 mcgms. of streptomycin per c.c. A blood serum level of 16 mcgms. could be obtained by 0.4 grams of streptomycin intramuscularly four-hourly.

Two typhoid carriers, both asymptomatic, received combined oral and systemic streptomycinfor ten days. In both instances, the drug failed to eliminate the typhoid organisms from the faeces. One patient in whom periostitis and osteitis of the right tibia developed four months after apparent recovery from typhoid fever and in whom biliary drainage culture was positive, was given streptomycin therapy for ten days and was apparnetly cured. In their opinion - "Parenteral streptomycin alone is of no value as an adjuvant in the therapy of typhoid fever and in elimination of undetermined foci in the asymptomatic typhoid carrier." They suggested, however, that a trial be made of a dosage of 0.5 grams intra-muscularly three-hourly, together with 1 gram by mouth six-hourly for ten days in order to establish a final assessment of the value of streptomycin in typhoid fever.

CHLOROMYCETIN.

In 1949, Collins and Finland treated three cases of typhoid fever with 2,4 and 6 grams per day of chloromycetin for approximately two weeks. Of the three cases, one relapsed after two weeks and one showed faecal bacilli during convalescence. In their opinion, "Although it may have had a beneficial effect on the course of the acute disease, it did not produce the dramatic results that were expected."

2 grams per day for two weeks failed to cure a chronic typhoid carrier where the gall-bladder had been removed.

In 1949, Rumball & Moore reported the failure of chloromycetin in the carrier state.

In 1950, Stryker reported the treatment of a single carrier. The results with chloramphenicol drug therapy he considered to be encouraging, although positive stool and bile cultures returned on cessation of thecourse, which consisted of 5 grams followed by 0.5 grams two hourly for ten days, then 4 hourly for four days. (Total 80 grams.) His conclusion was that, "The well-documented beneficial results in acute typhoid fever stand in contrast to those in the chronic carrier state."

In 1950, Douglas reported three cases of acute typhoid fever in adult mental hospital patients, treated by chloramphenicol. One case was given 31 grams in 16 days for an acute attack and 24.75 grams in 13 days for the relapse. Two of the three cases became chronic carriers. In one case there had been delay in starting the therapy. The other had 32.5 grams in 14 days. On the 63rd day she had a rigor and the following day jaundice of obstructive type. Douglas suggested that the jaundice was probably due to a gall-stone but, (Author) it seems equally likely to have been due to cholangitis and this may have been an indication of the development of the carrier state. A further 25.5 grams of chloramphenicol was given at this stage.

In 1950, Woodward et al., in a well documented paper, discussed the treatment of twenty-four patients with typhoid fever treated by chloramphenicol. With justification, they stated that chloramphenicol was a valuable therapeutic agent in the treatment of typhoid fever. No patient became a carrier.

Note. Chloramphenicol was found in the bile of carriers in concentrations of 50% of blood levels.

Woodward et al. record that concentrations as high as 1,000 gamma per c.c. had no detectable in vitro bactericidal effect on S. typhi. Therefore they considered that the poor results in carriers should have been expected.

Four carriers were treated with massive doses of chloromycetin for a two week period. (The initial dose was

60 mgms. per k.b.w. followed by 4 to 6 grams per day. Each received an average of 71 gtams over 15 days.) The writers concluded that the drug was "consistently unsatisfactory in eradicating the carrier state."

In 1952, Levin et al. reported the successful treatment of a carrier by chloramphenicol.

In 1951, Kennedy and Millar described a urinary carrier of S. paratyphi B. treated with chloramphenicol and cured with 1 gram t.i.d. for ten days. He had been resistant to penicillin, sulphaguanidine, sulphadiazine, sulphadimidine, Mandelix and streptomycin.

TERRAMYCIN.

In 1951, Korns & Albrecht recorded the treatment of thirteen chronic typhoid carriers with terramycin, (1.25 grams orally six-hourly for ten days) without success.

OTHER RECENT METHODS.

In 1948, Korns et al. reported the treatment of twenty-one chronic carriers of typhoid with the tin compound heptadekylaldehyde stannoxysterate. They failed to demonstrate any effect on the presence of S. typhi in the stools. They gave penicillin and sulphathiazole to eight chronic typhoid carriers and found that the typhoid bacilli disappeared from the stool in each individual. In two instances the organisms were absent from the stools for at least two weeks following the discontinuance of treatment. They re-appeared, however, in the stools of all carriers.

In 1950, in a massive paper Vaichulis et al. stated that the criteria of cure in Illinois were eight negative faecal cultures at 30-day intervals, plus two negative bile cultures, 7 days apart, 30 days after the last stool examination.

In a study of the bacterial flora in milk, Vaichulis observed that contamination by certain gram-positive, aerobic, mesophilic, spore-forming bacilli was accompanied by the presence of comparatively few gram negative bacteria. Activity against S. typhi was demonstrated on agar plates. Similar typhoid-inhibiting organisms were then isolated from the stools of patients in whom the carrier state had become cured spontaneously.

The organism was thought to be a strain of B. subtilis. They fed those to twenty-five chronic typhoid carriers and claimed cure in 19 (76%).

They also made a trial of "synergistic therapy" A solution of penicillin, carinamide and sulphonamide in 5% ethyl alcohol was given intra-venously in seventeen cases, definite cure resulting in three cases receiving large amounts (18%).

Promin was given to six cases. The results were unsuccessful.

Aureomycin was given to two cases. The results were unsuccessful.

Chloromycetin was given to two cases. The results were unsuccessful.

Terramycin was given to one case. The result was unsuccessful.

P/38 (Schering) and 5,10 - D. (Ganes Chem. Works) were given to eight cases. The results were uniformly unusccessful.

Streptomycin intra-muscularly and orally (simultaneously) was possibly successful in one of three cases.

Vaichulis et al. recommend cholecystectomy if calculi are seen and state that, if the gall-bladder is not visualised after several attempts, cholecystectomy will be required in most cases.

In an addendum to this paper the results in 116 carriers were reviewed.

Spontaneous cure occurred in - - - - - -	41
Cholecystectomy alone cured - - - - - -	13
Cholecystectomy + bacillus therapy cured -	15
Bacillus therapy alone cured - - - - - -	21
Other methods cured - - - - - - - - - -	26

THE POSITION OF NEOMYCIN IN RELATION TO ENTERIC ORGANISMS.

This antibiotic was introduced by Waksman et al. in 1949 and was found to be active against S. typhi in mice.

In 1950, Felsenfeld et al. compared the in vitro and in vivo effectiveness of neomycin with that of the other antibiotics such as streptomycin, chloromycetin, aureomycin and polymixin. 370 organisms were tested. Neomycin was found to have a favourable (strong) action on gram negative rods and had a broad range of activity in relatively small amounts against the enterobacteriaceae.

In 1950, Welch et al. compared the effect of nine antibiotics on experimental typhoid infections in mice. They found their results to be anomalous when compared to reported clinical trials. In general, the polypeptide antibiotics "do not appear to be promising because they are not absorbed to any appreciable extent from the gastrointestinal tract and their inherent toxicity precludes their usefulness if given parenterally." Next in order of effectiveness came streptomycin, dihydrostreptomycin aureomycin, neomycin, aureotracin, penicillin and last, chloramphenicol. Contrary to these results, however, they stated that chloramphenicol was far superior to any of the other antibiotics which had been used in the treatment of typhoid fever in man. They concluded that their tests demonstrated, "The fallacy of accepting the efficacy of certain antibiotics solely on the date presented from a limited type of in vivo animal test."

In 1950, Jackson et al. carried out in vitro studies of the relative sensitivities of the salmonella group of organisms. They pointed out that:-

1. Many facts may profoundly influence the quantitative results although the conditions are uniform.

2. The interpretation of the results in terms of clinical effectiveness likewise requires considerable caution. e.g. factors such as absorption, excretion, diffusion and plasma-binding and some of the characteristics of the infection itself may effect the activity of the different agents in vivo.

3. Therefore their findings could only be useful as a general approximation of the relative usefulness of these agents in chemotherapy.

The order of activity of the different antibiotics for the salmonellas was given as:-

Polymyxin.
Aerosporin.
Chloromycetin.
Terramycin and penicillin.
Aureomycin.
Streptomycin.
Bacitracin.

Only a few strains were tested for neomycin and terramycin sensitivity. Wide ranges of partial inhibition were observed in the tests with both of these new antibiotics.

In a personal communication, Hicks (1958) gave the sensitivity of S. typhi to neomycin as 0.1 to 5.0 mcg. per ml. and that of S. paratyphi as 0.31 to 20 mcg. per ml.

It will thus be seen that, while in vitro tests indicate a certain amount of activity of neomycin towards the enteric organisms, the clinical effect of the antibiotic is not yet assessed. It seems, however, that only 3% of the oral dose is absorbed and that parenteral administration is virtually contra-indicated because of the high incidence of severeototoxic and nephrotoxic side-action.

RESULTS OF MEDICAL TREATMENT OF ENTERIC CARRIERS.

The following tables have been extracted from the literature.

SULPHAGUANIDINE.

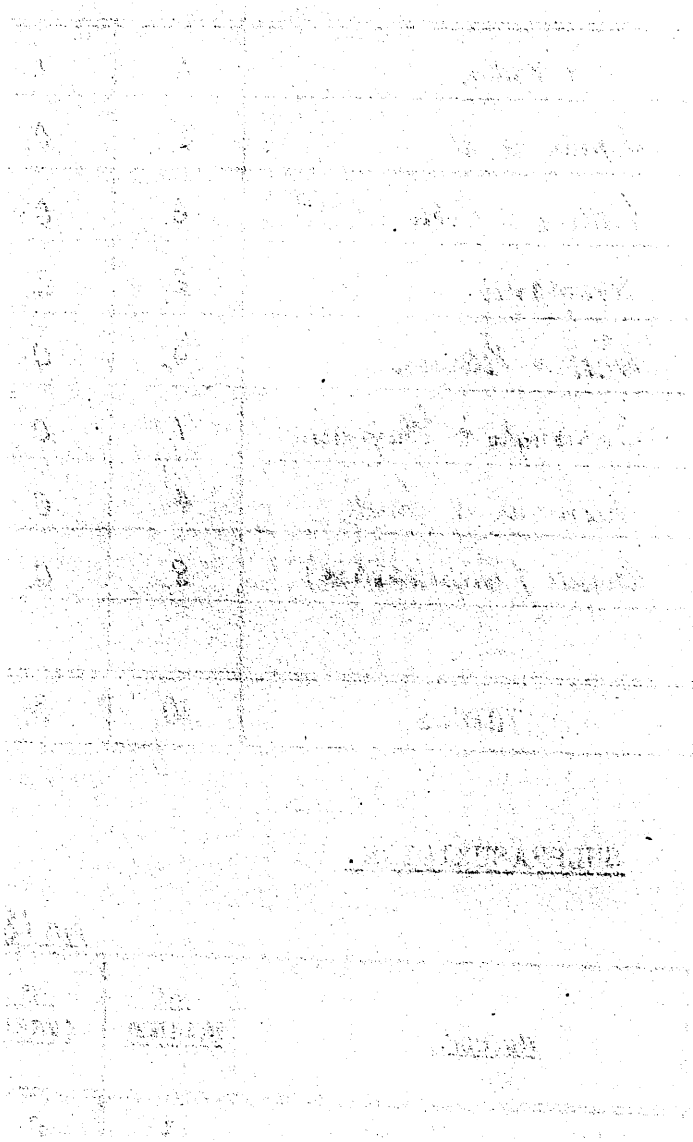
FIG. 17.

YEAR.	AUTHOR	Nº TREATED	Nº CURED.	
1941.	Levi & Willen.	1.	1.	
1942.	Saphir et al.	5.	0.	
1942.	Cutting & Robson.	6.	0.	
1942.	Hoaglund.	2.	2.	(VERY SHORT FOLLOW-UP).
1942	Watt & Peterson.	3.	0.	
1943.	Burroughs & Grayham.	1.	0.	
1945.	Rheinstein & Smith.	4.	0.	
1954	Russell (unpublished).	8.	0.	
	TOTALS.	30.	3.	

SULPHASUXIDINE.

FIG. 18.

YEAR.	AUTHOR.	Nº TREATED.	Nº CURED.
1942.	Kirby & Rantz.	3.	0.
1945.	Rheinstein & Smith.	4.	0.
	TOTALS.	7.	0.



SULPHADIAZINE.

FIG. 19.

YEAR.	AUTHOR.	Nº TREATED	Nº CURED.
1942.	Cutting & Robson.	6.	0.
1946.	Rivers et al.	1.	0.
	TOTALS.	7.	0.

PENICILLIN & SULPHAMERAZINE.

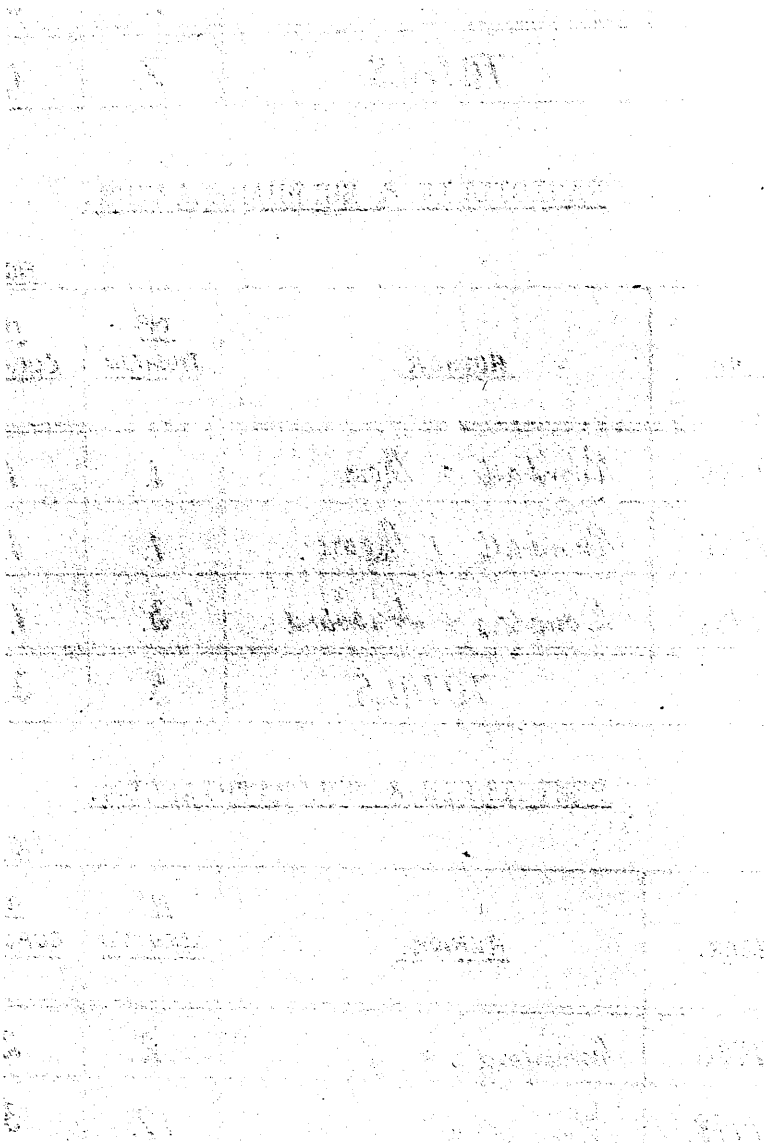
FIG. 20.

YEAR	AUTHOR.	Nº TREATED	Nº CURED.
1949.	Rumball & Moore.	1.	1.
1950.	Rumball & Moore.	1.	1.
1951.	Douglas & Hubbard.	3.	1.
	TOTALS.	5	3.

PENICILLIN & SULPHATHIAZOLE.

FIG. 21.

YEAR.	AUTHOR.	Nº TREATED	Nº CURED
1946.	Comerford et. al.	2.	2.
1948.	Fry et al.	17.	3.
1948.	Korns et al.	8.	0.
1949.	Bigger & Daly.	9.	3.
	TOTALS.	36.	8



PENICILLIN.

FIG. 22.

YEAR.	AUTHOR	Nº TREATED	Nº CURED
1946.	Rivier et al.	1.	1.

STREPTOMYCIN.

FIG. 23.

YEAR.	AUTHOR	Nº TREATED	Nº CURED.	
1945.	Rutstein et al.	3.	2.	(TRANSITORY EFFECT ONLY).
1947.	Pulaski & Amspacker.	2.	0.	
1950.	Vaichulis et al.	3.	?1.	
	TOTALS.	8.	1.	

AUREOMYCIN.

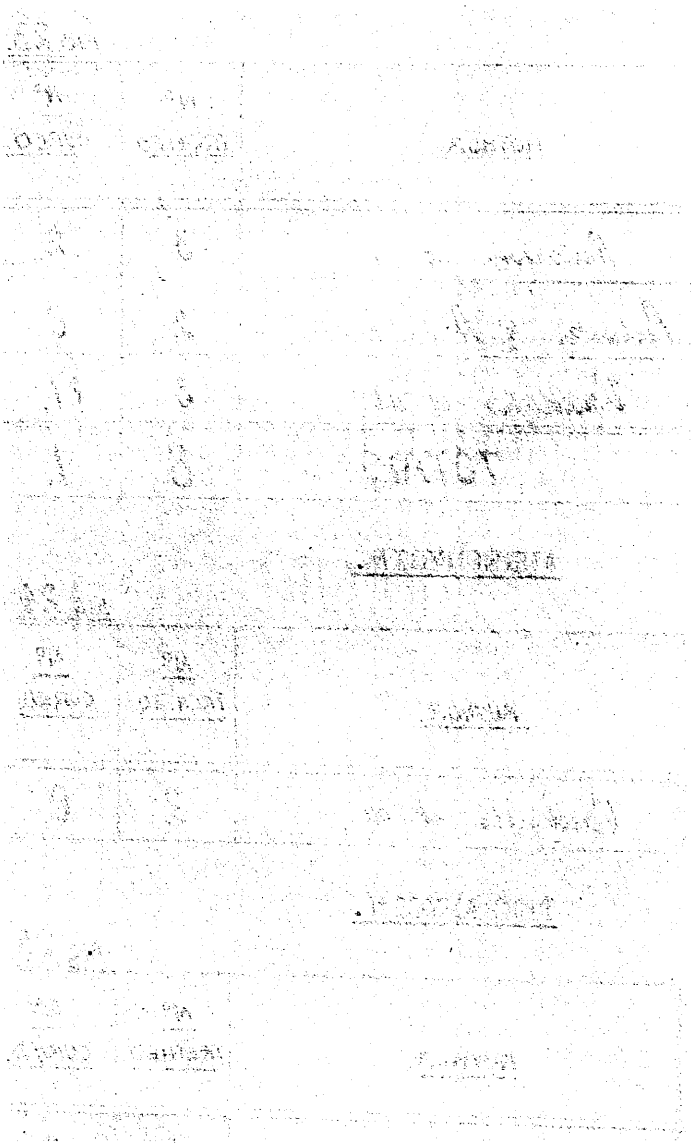
FIG. 24.

YEAR.	AUTHOR.	Nº TREATED	Nº CURED.
1950.	Vaichulis et al.	2.	0.

TERRAMYCIN.

FIG. 25.

YEAR.	AUTHOR.	Nº TREATED	Nº CURED.
1950.	Vaichulis et al.	1.	0.
1951.	Korns & Albrecht.	1.	0.
	TOTALS.	2.	0.



CHLORAMPHENICOL.

FIG. 26.

YEAR.	AUTHOR	Nº TREATED	Nº CURED.
1949.	Collins & Yinland.	1.	0.
1949.	Pearson & Wolffe.	1.	0.
1950.	Stryker.	1.	0.
1950.	Rumball & Moore.	1.	0.
1950.	Woodward et al.	4.	0.
1950.	Vaichulis	2.	0.
1955.	Middlestone & Murphy.	1.	0.
1954.	Lemmon et al.	4.	0.
1954.	Flynn.	6.	0.
	TOTALS.	21.	0.

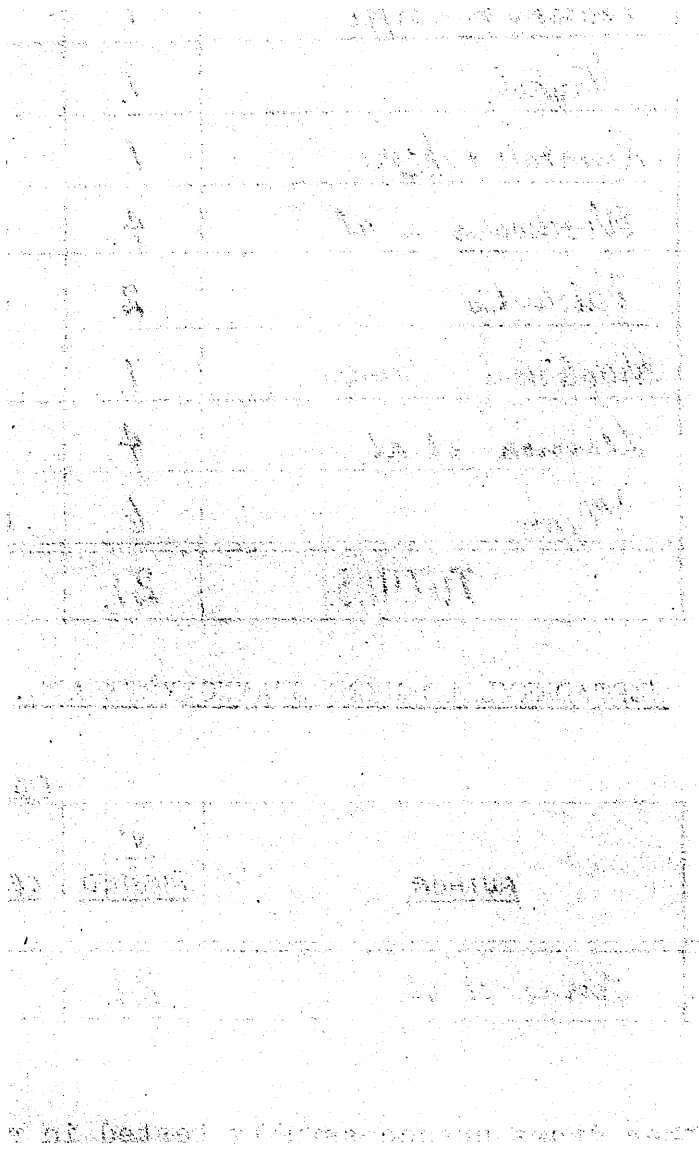
HEPTADEKYLALDEHYDE STANNOXYSTERATE.

FIG. 27.

YEAR	AUTHOR	Nº TREATED	Nº CURED
1948.	Korns et al.	21.	0.

Other drugs unsuccessfully tested in recent years are ---- Promin, P. - 38 (Schering) and 5, 10 - D. (Ganes Chem. Works.).

An analysis of the above tables follows:-



RESULTS OF TREATMENT BY SULPHONAMIDES.

FIG. 28.

THERAPEUTIC AGENT.	Nº OF CASES TREATED.	Nº OF CURES.
Sulphaguanidine.	30	3.
Sulphasuxidine.	7.	0.
Sulphadiazine.	7.	0.
TOTALS.	44.	3.

RESULTS OF TREATMENT BY PENICILLIN & SULPHONAMIDES.

FIG. 29.

THERAPEUTIC AGENT.	Nº OF CASES TREATED	Nº OF CURES
Penicillin + Sulphathiazole	36.	8.
Penicillin + Sulphamerazine	5.	3.
TOTALS.	41.	11.

RESULTS OF TREATMENT BY ANTIBIOTICS.

FIG. 30.

ANTIBIOTIC	Nº OF CASES TREATED	Nº OF CURES.
Penicillin.	1.	1.
Streptomycin.	8	2.
Aureomycin.	2	0.
Terramycin.	2	0.
Chloramphenicol.	21.	0.
TOTALS.	34.	3.

SUMMARISING THE RESULTS OF MODERN CHEMOTHERAPY AND ANTIBIOTIC THERAPY IN THE ALIMENTARY ENTERIC CARRIER, IT IS APPARENT THAT OF 119 CARRIERS SO TREATED, ONLY 17 (approx. 14%) HAVE BEEN CURED. THE HIGH HOPES HELD OUT FOR MODERN MEDICAL TREATMENT HAVE THEREFORE, SO FAR, NOT BEEN SUBSTANTIATED.

S E C T I O N 1V.

The results of treatment in the nine carriers.

THE RESULTS OF TREATMENT IN THE NINE CARRIERS.

Figure 32 shows that following a course of oral neomycin there seemed to be some diminution in faecal excretion of enteric organisms but it was only after all carriers had had cholecystectomy performed that faecal excretion was abolished. Case No. 2 produced a positive culture in February 1959 and is still under surveillance. His further observation and treatment are considered in detail in Section V11. It is hoped that he too will eventually become negative.

Neomycin appears to have had some effect in reducing the excretion frequency of enteric organisms but the main factor in cure was the removing by cholecystectomy of the prime continuing source of infection. There seems reason to believe that a post-operative course of neomycin may shorten the period of post-operative persistence of excretion which sometimes occurs. On the other hand since only 3% of the oral dose is believed to be absorbed the drug probably has its action locally in the bowel where it kills those organisms excreted with the bile.

The mortality rate in the series has been nil and there has been no significant morbidity. On the contrary there is no doubt in the mind of the writer and of several independant observers that the general state of health of the patients is considerably improved. The carrier ward is now a cheerful place to enter and the patients have an air of psychological uplift and expectant optimism.

Note. 1. In order to satisfy the criteria demanded by the Medical Officer of Health, the patients will continue to be segregated until they have had twelve consecutive negative monthly stool cultures, after which they will be allowed to mix with other patients in the hospital.

Note. 2. In actual fact in the present series post-operative stool cultures were made fortnightly and not monthly as indicated.

AVERAGE MONTHLY NUMBER OF POSITIVE STOOL CULTURES IN THE GROUP OF CARRIERS

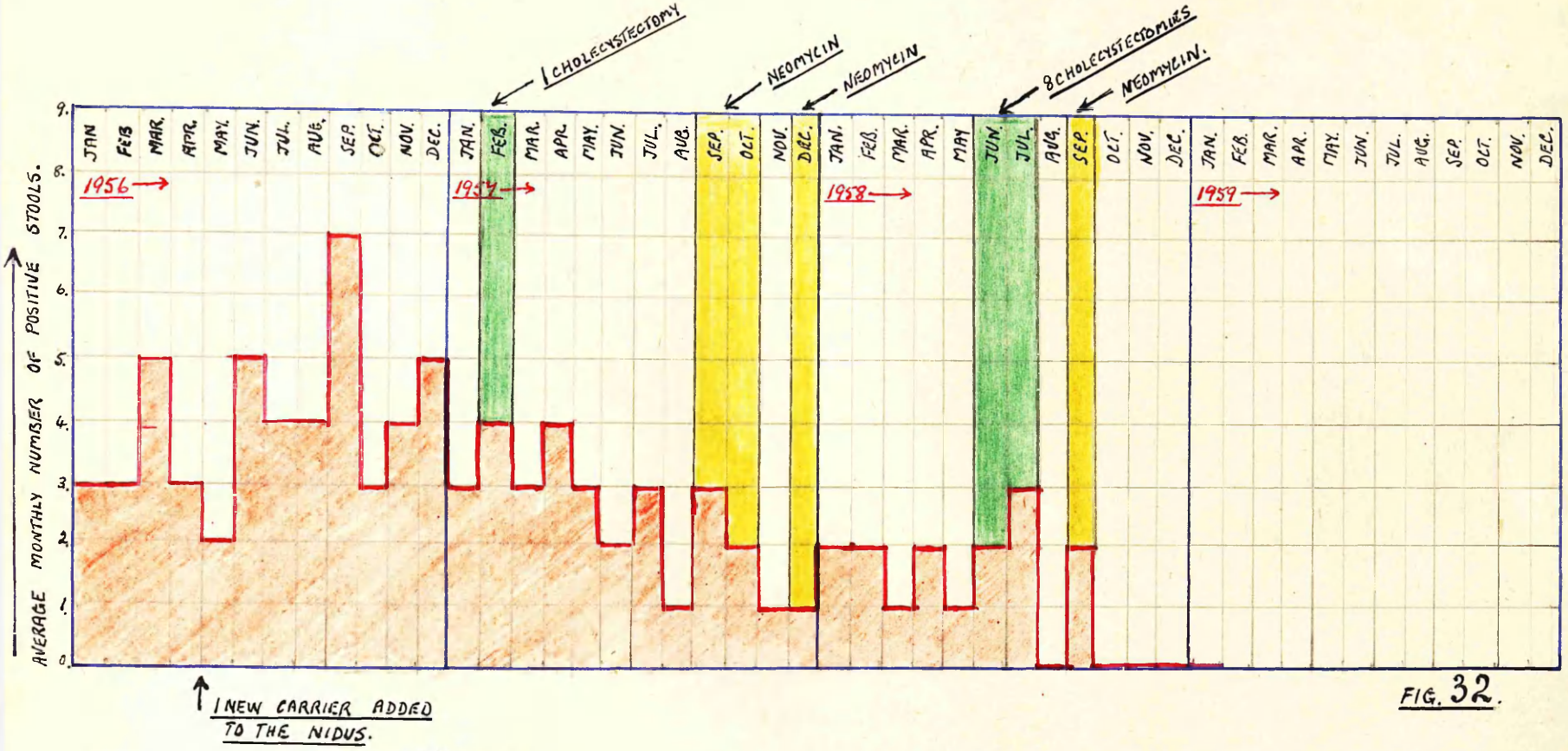
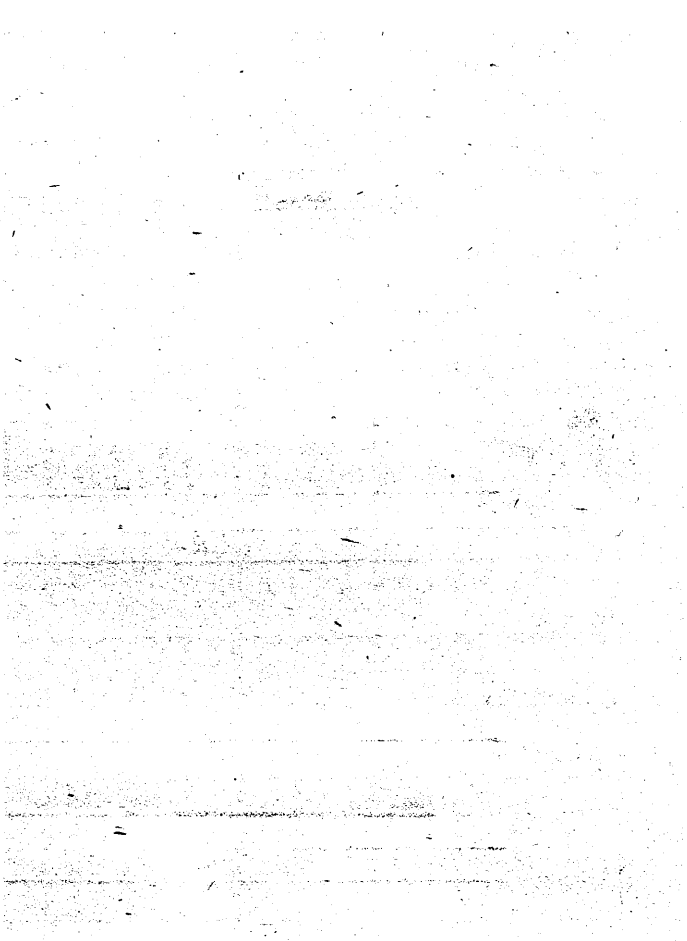


FIG. 32.

Effects of :-

1. Addition of a new carrier.
2. A single cholecystectomy.
3. Courses of Neomycin.
4. 8 cholecystectomies.
5. Post-operative course of Neomycin.



S E C T I O N V.

Analysis of the results of the investigations performed.

The significance of "Excretion Frequency".

Its relation to loss of function and pathological change in the gall-bladder.

The immediate effect of cholecystectomy on faecal excretion of enteric organisms.

The prospects for spontaneous cure.

EXCRETION FREQUENCY OF THE CARRIER STATE.

The excretion frequency of the carrier state from January, 1956, to the time of cholecystectomy in each of the nine carriers can be estimated from the relative numbers of positive and negative stool cultures. The number of positive cultures is expressed below as a percentage and when this figure is allotted to each carrier, they can be arranged in descending order of excretion frequency.

FIG. 33.

CASE Nº	PATIENT	RELATIVE NUMBERS OF POSITIVE + NEGATIVE STOOL CULTURES (PRE-OP).	EXCRETION % FREQUENCY.
1.	M.S.	11./13.*	84.
2.	J.C.	25./30.	83.
3.	J.K.	16./30.	53.
4.	H.McM.	10./30.	33
5.	D.S.	7./30.	23.
6.	J.Cr.	4./29.	14.
7.	T.B.	3./29.	10.
8	H.McD.	3./30	10.
9.	W.F.	2./26.	8.

* - MONTHLY STOOL CULTURES.

It seems pertinent to ascertain whether the severity of the infection in the different carriers, as evidenced by their excretion frequency, bears a significant

relationship to the following features which have been recorded for each carrier.

1. Pre-operative tests of liver function.

2. Radiological evidence of pathological changes in the gall-bladder and bile-ducts.

    a) Function on oral cholecystography.

    b) Function on intra-venous cholecystography.

    c) Stones or alterations of size or shape of the gall-bladder.

3. Evidence at operation of pathological changes in the gall-bladder and bile-ducts.

    a) Adhesions.

    b) Stones.

    c) Chronic or acute cholecystitis.

    d) Changes in appearance of common bile-duct.

    e) Results of culture of bile from common bile-duct.

4. Macroscopic and microscopic features of the excised gall-bladders.

PRE-OPERATIVE EXCRETION FREQUENCY RELATED TO

RESULTS OF TESTS OF LIVER FUNCTION.

FIG. 34.

CASE Nº	PATIENT.	PRE-OPERATIVE EXCRETION FREQUENCY.	SERUM BILIRUBIN mgm/100 ml.	SERUM ALKALINE PHOSPHATASE K+A units.	THYMOL TURBIDITY Units.	TOTAL PLASMA PROTEIN. gm/100 ml.
1.	M.S.	84.	10·5	32.	7.	7.
2.	J.C.	83.	0·8	8	3	7.
3.	J.K.	53	1·0	6	2	7.
4.	H.M'M.	33.	0·8	6	2	7.
5	D.S.	23.	0·8	5	4	7·5.
6	J.Cr.	14.	1·0	12	2	6·75.
7.	T.B.	10.	0·2	7	3	8·5.
8	H.McD.	10.	0·2	9		8.
9.	W.F.	8.	0·2.	6	1	8.

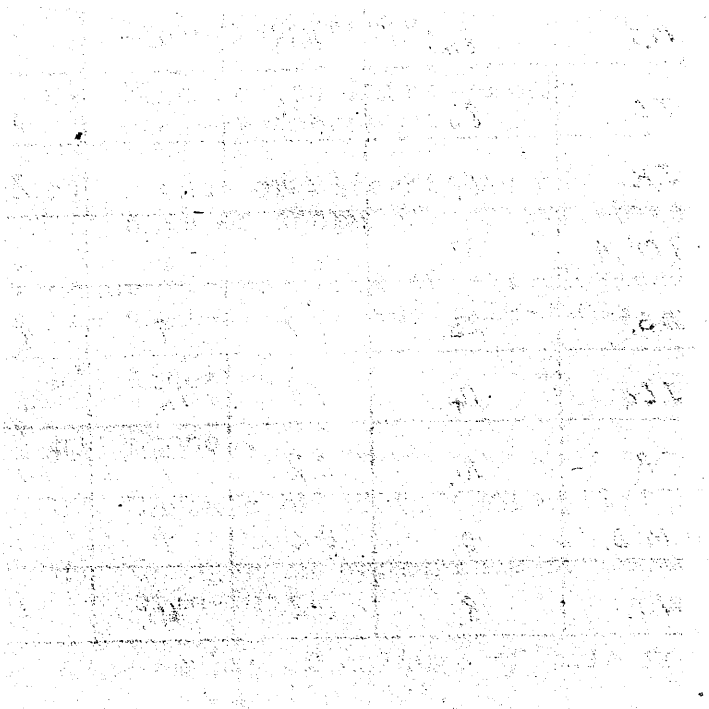
COMMENTS.

The first case should be excluded since he had obstructive jaundice when the blood was withdrawn.

1. There is a relatively higher serum bilirubin level in the more persistent carriers.

2. The plasma protein level is slightly lower in the more persistent carriers.

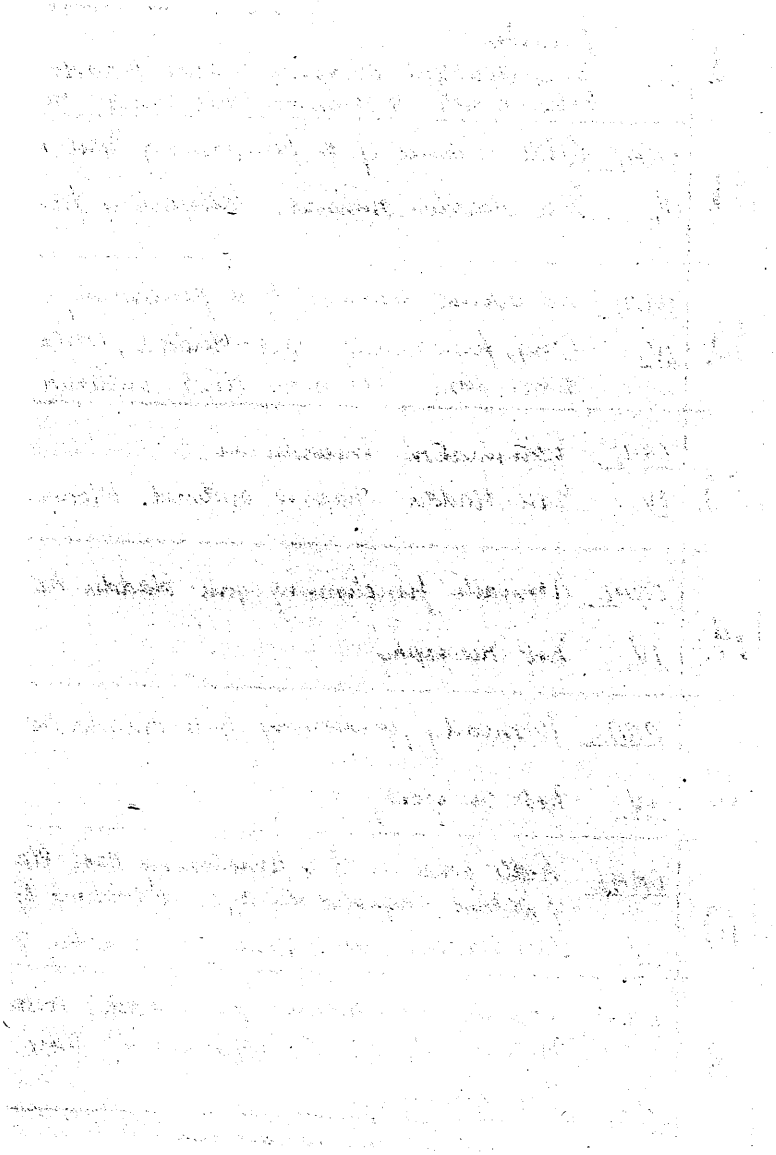
3. Serum alkaline phosphatase and thymol turbidity tests show no significant relationship to persistence. (excretion frequency.)



SUMMARY OF RADIOLOGICAL STUDIES AND COMPARISON WITH EXCRETION FREQUENCY OF THE CARRIERS.

FIG. 35.

CASE NO	PATIENT	Ex.F.	RADIOLOGICAL FINDINGS.
1.	M.S.	84.	Obstructive Jaundice. Cholecystography not performed.
2.	J.C.	83.	ORAL. Inadequate visualisation. Little evidence of gall-bladder function I.V. Very doubtful evidence of gall-bladder shadow. Extra-hepatic & common bile ducts outlined
3.	J.K.	53.	ORAL. Little evidence of a functioning gall-bladder. I.V. Gall-bladder outlined. Satisfactory function.
4.	H.M'M.	33.	ORAL. No definite evidence of a functioning gall-bladder. I.V. Long, functioning gall-bladder, containing small dense stone. Common duct outlined.
5.	D.S.	23.	ORAL. Examination inconclusive. I.V. Gall-bladder shadow outlined. Moderate function.
6.	J.Cr.	14.	ORAL. Normally functioning gall-bladder. No evidence of stone. I.V. Not necessary.
7.	T.B.	10.	ORAL. Normally functioning gall-bladder. No evidence of stone. I.V. Not necessary.
8.	H.M'D.	10.	ORAL. Little evidence of a functioning gall-bladder (Doubtful if patient ingested the dye. No evidence of dye in bowel). I.V. Gall-bladder well outlined. Reasonably normal function
9.	W.F.	8.	ORAL. Normally functioning gall-bladder with outlining of common duct. No evidence of stone. I.V. Not necessary.
			Ex.F. - EXCRETION FREQUENCY ORAL - ORAL CHOLECYSTOGRAPHY. I.V. - INTRA-VENOUS CHOLECYSTOGRAPHY.



COMMENTS ON RADIOLOGICAL FINDINGS.

Case No. 1 was jaundiced and a straight X-ray only was carried out.

1. On plain X-ray and oral and intra-venous cholecystography, a single stone was demonstrated in only one case. These findings were shown at operation to be valueless in that stones were found in three cases. (Cases Nos. 2,3 and 4.)

2. On oral cholecystography, the three most persistent carriers were found to show little or no gall-baldder function.

   Case No. 8 may not have ingested the dye and showed no gall-bladder function.
   Case No. 5 had a slightly high serum bilirubin and may have had a degree of cholangitis at the time of examination. The remaining cases (Nos. 6,7 and 9) all showed normally functioning gall-bladders.

3. In those cases in which little or no function was shown on oral cholecystography, intra-venous cholecystography was performed. In only one case -- a very persistent carrier did it fail to outline the gall-bladder.

4. Three gall-bladders were shown to be enlarged (Cases Nos. 3,4 and 5) and this was shown later at operation to be significant.

CONCLUSIONS.

1. The loss of function of the gall-bladder as shown on cholecystography is directly related to the excretion frequency.

2. Oral cholecystography is a more sensitive test of function (if properly performed) than the intra-venous method.

NOTE.

The radiological reports were given by a radiologist who had no knowledge of the clinical details of the individual cases and were therefore quite unbiased.

GRADED RADIOLOGICAL FINDINGS RELATED TO EXCRETION FREQUENCY.

The radiological findings have been separated into 4 grades corresponding to function as follows:-

Normal function on oral cholecystography. ----- Grade 1

Doubtful function on oral cholecystography.) Normal function on intra-venous cholecystography.) ----- Grade 11

No function on oral cholecystography.) Normal function on intra-venous cholecystography.) ----- Grade 111

No function on oral cholecystography.) Doubtful function on intra-venous cholecystography.) ----- Grade 1V

Fig. 36.

Case No.	Patient.	Excretion frequency.	Grade.
2.	J.C.	83	1V
3.	J.K.	53	111
4.	H.McM.	33	11
5.	D.S.	23	11
6.	J.Cr.	14	1
7.	T.B.	10	1
8.	H.McD.	10	?111
9.	W.F.	8	1

Case No. 1 (M.S.) has been excluded since he had obstructive jaundice and therefore did not have cholecystography.

CONCLUSIONS.

The grades of function are seen to follow closely the excretion frequency.

The gall-bladders showing poorest function are associated with a high excretion frequency.

The gall-bladders which show moderate function are associated with an intermediate excretion frequency.

The gall-bladders which show good function are associated with a low excretion frequency. (Case No. 8 is the only exception and here it is doubtful whether the patient ingested the oral dye.)

EXCRETION FREQUENCY RELATED TO OPERATIVE FINDINGS.

FIG. 37.

CASE No.	PATIENT	E.F.	OPERATIVE FINDINGS.
1	M.S.	84.	Distorted, fibrotic, subacutely inflamed gall-bladder and bile-duct system, buried in dense adhesions. Duodenum adherent to gall-bladder. Right hepatic duct had probably been partially obstructed by adhesions. Cholecystectomy difficult.
2	J.C.	83.	Small, fibrotic, "intra-hepatic" gall-bladder, embedded in adhesions, containing one stone. The gall-bladder had obviously been the seat of fairly acute and persistent infection. Common bile-duct greatly distended. Cholecystectomy difficult.
3	J.K.	53.	Gall-bladder greatly distended and full of faceted stones. Common bile-duct normal.
4.	H.McM.	33.	Very large gall-bladder to which omentum was adherent, and containing one stone. The gall-bladder had been the seat of chronic inflammation. Common bile-duct normal.
5.	D.S.	23.	Large, tense gall-bladder, somewhat adherent, but otherwise not remarkably abnormal. No stones. Common bile-duct normal.
6.	J.Cr.	14.	Adhesions around Hartmann's pouch and cystic duct. Otherwise no abnormality. No stones. Common bile-duct normal
7.	T.B.	10	Adhesions around base of gall-bladder. Organ otherwise normal. No stones. Ducts normal.
8.	H.McD.	10	Omentum adherent to gall-bladder at neck and fundus, but otherwise normal appearance. No stones. Common bile-duct normal.
9.	W.F.	8.	Gall-bladder and ducts normal in appearance. No stones.

E.F. - EXCRETION FREQUENCY.

CONCLUSION.

1. The excretion frequency is directly related to the chronicity and severity of the infection. The table shows that this relationship is remarkably accurate.

2. There can surely be no doubt that S. paratyphi B. in carriers, multiplies within the extra-hepatic biliary system, and that the degree of infection is directly related to the excretion frequency.

NOTE. The operation notes were written without knowledge of the excretion frequency of the carriers and were therefore without bias.

PRE-OPERATIVE EXCRETION FREQUENCY RELATED TO THE PRESENCE OF STONES IN THE GALLBLADDER AND TO POSITIVE CULTURES OF COMMON DUCT BILE.

FIG. 38.

CASE Nº	PATIENT.	PRE-OPERATIVE EXCRETION FREQUENCY %	STONES.	POSITIVE BILE CULTURE.
1.	M.S.	84.	HIGHLY ACUTE CHOLECYSTITIS	+
2.	J.C.	83.	+	+
3.	J.K.	53.	+	+
4.	H. M^{c}M.	33.	+	+
5.	D.S.	23.	—	—
6	J.Cy.	14.	—	—
7.	T.B.	10.	—	—
8	H.M^{c}D.	10.	—	—
9.	W.F.	8.	—	—

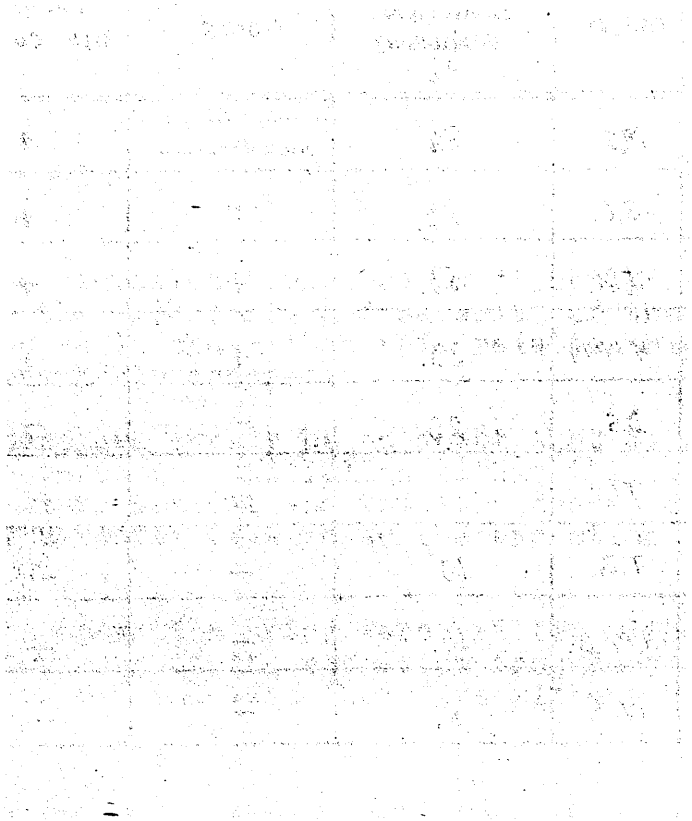
COMMENTS.

1. Apart from case No. 1 which showed a highly acute cholecystitis, the most persistently positive carriers showed one or more stones in the gallbladder.

2. Bile cultures from the common duct were positive in the four most persistently positive carriers.

CONCLUSION.

Living enteric organisms are found in the common bile-duct in the carrier state. They can be constantly cultured from this site in the most persistent carriers.



HISTOLOGICAL FINDINGS IN THE EXCISED GALL-BLADDERS RELATED TO EXCRETION FREQUENCY.

FIG. 39.

CASE Nº	PATIENT	EXCRETION FREQUENCY.	HISTOLOGY OF EXCISED GALL-BLADDER.
1.	M.S.	84.	Focal ulceration of mucosa. Dense infiltration of mucosa with chronic inflammatory cells. Areas of polymorph infiltration. Extension of inflammatory infiltrate between the muscle layers. SUBACUTE ULCERATIVE CHOLECYSTITIS.
2.	J.C.	83.	Degenerative change in mucosa which is atrophic. Remnants of mucosa densely infiltrated by chronic inflammatory cells, the infiltration extending fairly deeply to muscularis. Subserous + submucous fibrosis. CHRONIC CHOLECYSTITIS.
3.	J.K.	53.	Quite a marked diffuse chronic inflammatory infiltrate, especially in the mucous membrane. Some oedema between the muscle bundles. CHRONIC CHOLECYSTITIS.
4.	H.McM.	33.	Mucosa atrophic. Muscularis replaced by connective tissue. Foci of inflammatory infiltrate in the mucosa, indicative of continued infection. LOW-GRADE CHRONIC CHOLECYSTITIS.
5.	D.S.	23.	Gall-bladder wall very vascular. Sprinkling of chronic inflammatory cells in mucosa, spreading deeply via crypts. One aggregate of inflammatory cells. MILDLY CHRONICALLY INFLAMED GALL-BLADDER.
6.	J.Cr.	14.	Slight fibrosis of submucous, muscular and sub-serous coats. NO SIGN OF ACTIVE INFLAMMATION.
7.	T.B.	10	Mucosa thin and a little simplified. Partial fibrosis of muscularis SOME EVIDENCE OF PAST INFLAMMATION. NO SIGN OF RECENT ACTIVITY.
8.	H.McD.	10	General architecture normal. Gall-bladder thin-walled. Muscle probably congenitally poor. NO SIGN OF INFECTION, PAST OR PRESENT.
9.	W.F.	8.	Mucosal pattern complex. The wall showed – NO SIGN OF INFECTION, PAST OR PRESENT.

CONCLUSIONS.

1. The excretion frequency is directly related to the degree of inflammatory change in the gall-bladder wall. The constant faecal excretors show evidence of a chronic or acute-on-chronic inflammatory process. The intermediate excretors show evidence of mild chronic cholecystitis. The occasional excretors show virtually no evidence of the inflammatory process.

2. There is no evidence in the present series that the intensity of the inflammatory changes is related to the duration of the carrier state.

3. The changes are most marked at the mucous surface of the gall-bladder and fade as the serous surface is approached, suggesting that the gall-bladder is infected from the bile and not via the blood-stream.

EFFECT OF CHOLECYSTECTOMY ON FAECAL EXCRETION OF ENTERIC ORGANISMS WITH SPECIAL REFERENCE TO POST-OPERATIVE PERSISTENCE OR ACTIVATION OF INFECTION OF THE BILIARY TRACT.

← PRE-OP. | POST-OP. →

CASE Nº	PATIENT.	PRE-OP. EXCRETION FREQUENCY												
1.	M.S.	84.	+	+	+	+	+	+	+	+	+	+	−	−
2.	J.C.	83.	−	+	+	+	+	+	−	+	−	−	−	−
3.	J.K.	53.	+	−	−	−	−	−	−	+	−	−	−	−
4.	H.McM.	33.	+	+	−	+	−	−	+	−	−	−	−	−
5.	D.S.	23.	−	−	−	−	−	−	−	−	−	−	−	−
6.	J.Cr.	14.	−	−	−	−	−	−	+	+	−	−	−	−
7.	T.B.	10.	−	−	−	−	−	−	−	−	−	−	−	−
8.	H.McD.	10.	−	−	−	−	−	−	−	−	−	−	−	−
9.	W.F.	8.	−	−	−	−	−	−	−	−	−	−	−	−

± } MONTHLY STOOL CULTURES.

↑ CHOLECYSTECTOMY.

FIG. 40.

CONCLUSIONS.

1. The most-persistently positive carriers remain positive for a time after cholecystectomy.

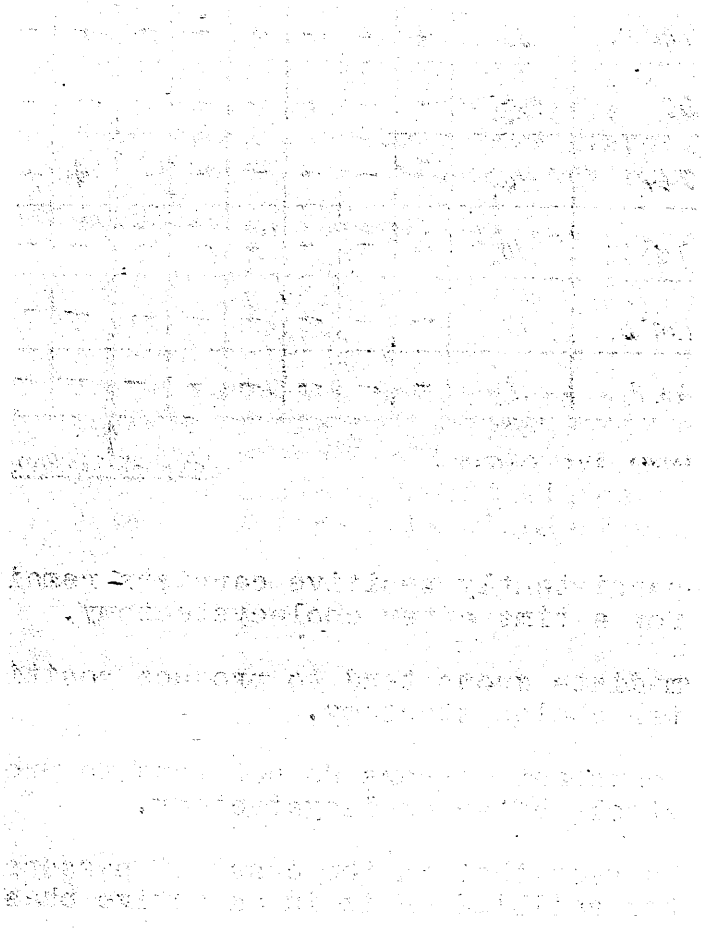
2. The intermediate group tend to produce positive stools after cholecystectomy.

3. The least constant passers do not tend to produce positive stools after cholecystectomy.

It would seem that in the constant passers the infection in the gallbladder is in an active phase and that the main site of infection is the gallbladder.

Residual infection gradually clears when the

gall-bladder has been removed. In the intermediate group removal of the gall-bladder tends to produce temporary infection in the bile ducts. In the quiescent carriers removal of the gall-bladder does not produce a period of infection in the bile ducts.



THE PROSPECT OF SPONTANEOUS CURE.

The mention in several papers of cases undergoing spontaneous cure led to a search of the old records of the eight carriers who had been resident in the hospital since 1951.

A survey of the monthly records of faecal cultures over the five-year period 1952 to 1956 for the eight carriers, shows no evidence whatever of a tendency to spontaneous cure.

S E C T I O N VI.

Further detailed consideration of the histology in those gall-bladders which were best preserved.

SECTION VI.

A detailed examination of the
ory in three parallel planes which
ast preserved.

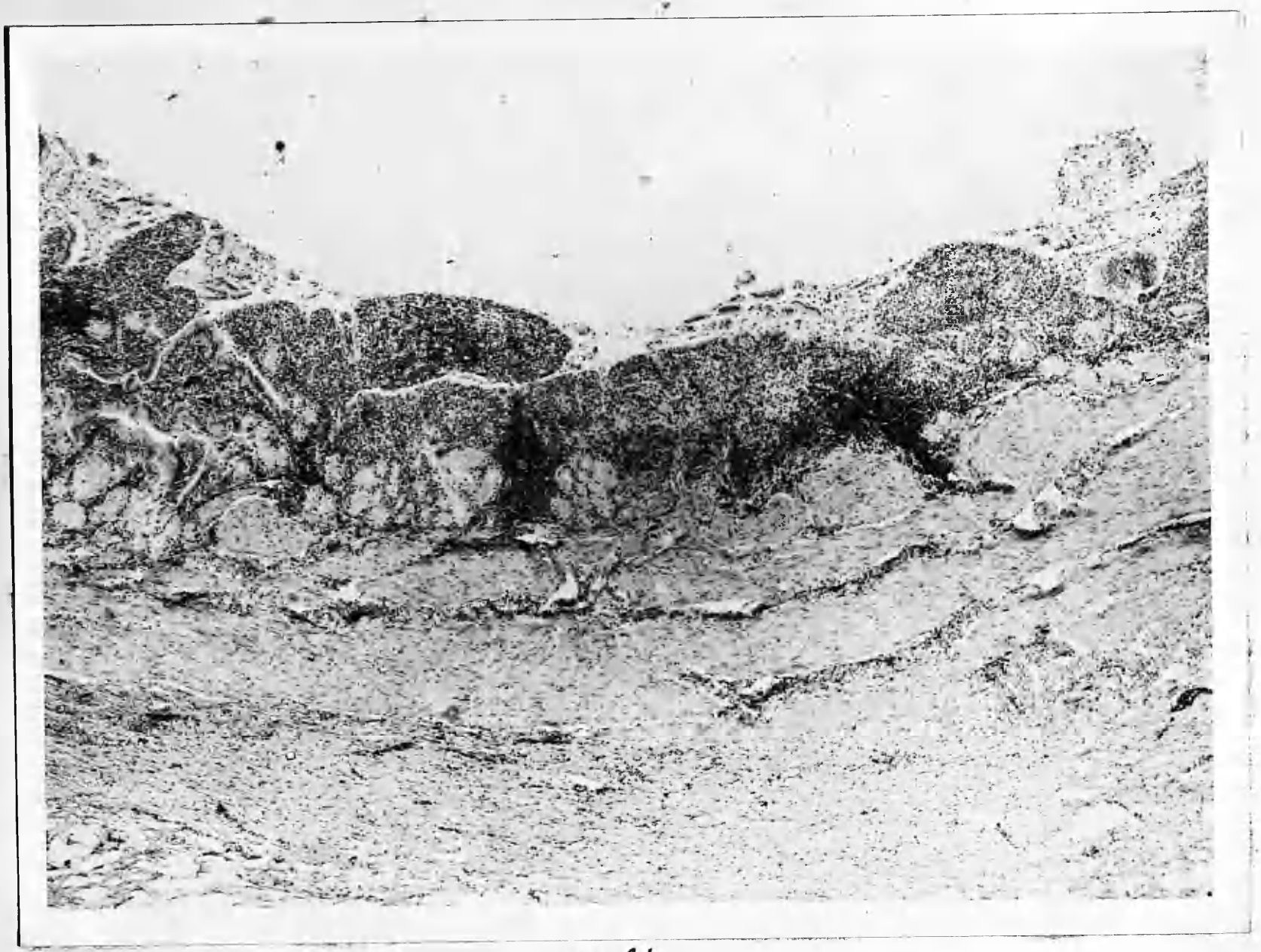


FIG. 41.

CASE No. 1 PATIENT M.S.

SECTION OF GALLBLADDER WALL AT FUNDUS. There is focal ulceration of the mucosa which is densely infiltrated with chronic inflammatory cells. Extension of the inflammatory infiltrate is seen between the muscle layers.

Sub-acute ulcerative cholecystitis.

(H. & E. x 30)

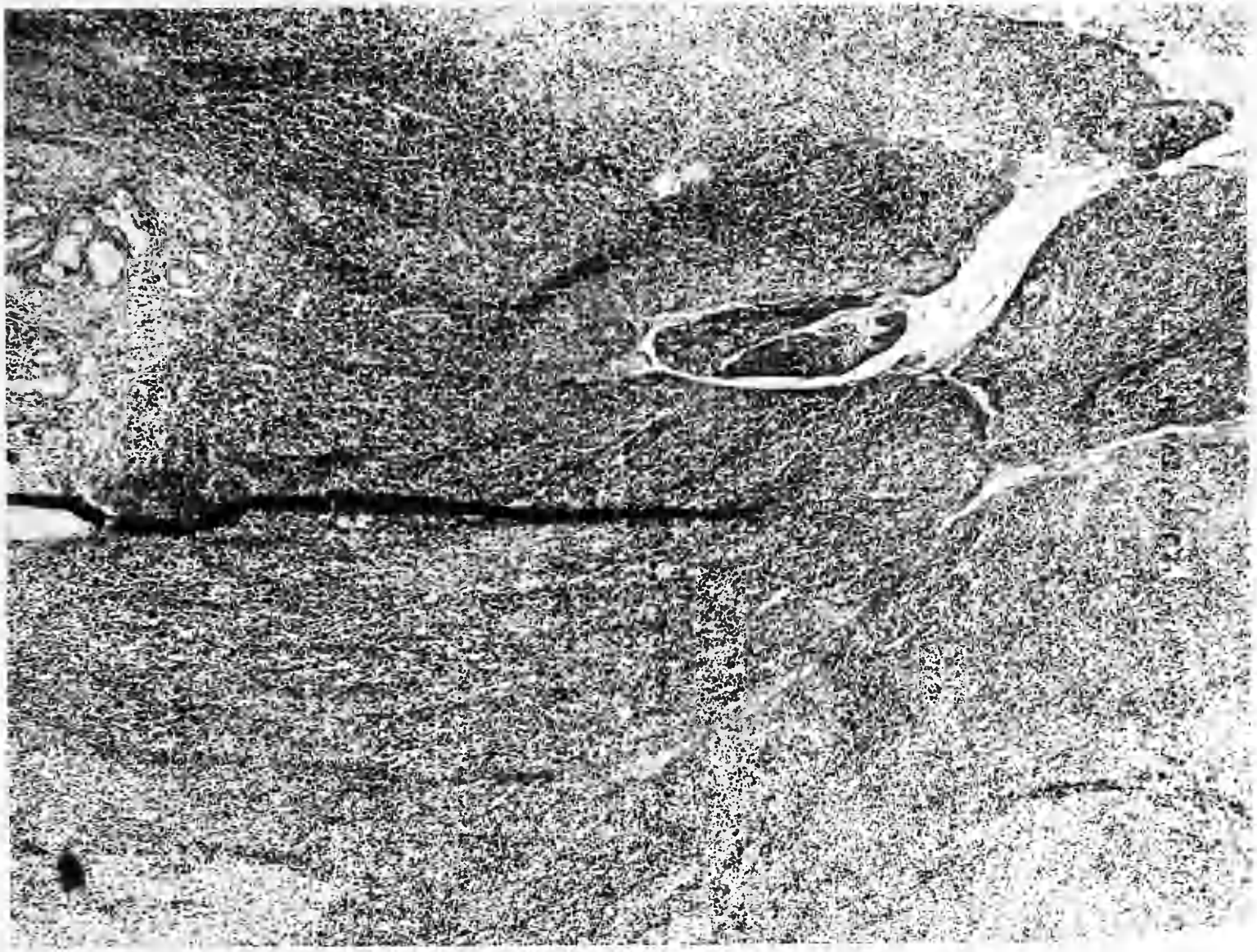


FIG. 42.

CASE No. 1 PATIENT M.S.

SECTION OF GALLBLADDER WALL AT NECK. Highly acute inflammation. The section shows the mucosal surface, densely infiltrated with inflammatory cells and a patch of necrotic fibrin in the lumen.

Acute cholecystitis.

(H. & E. x 30)

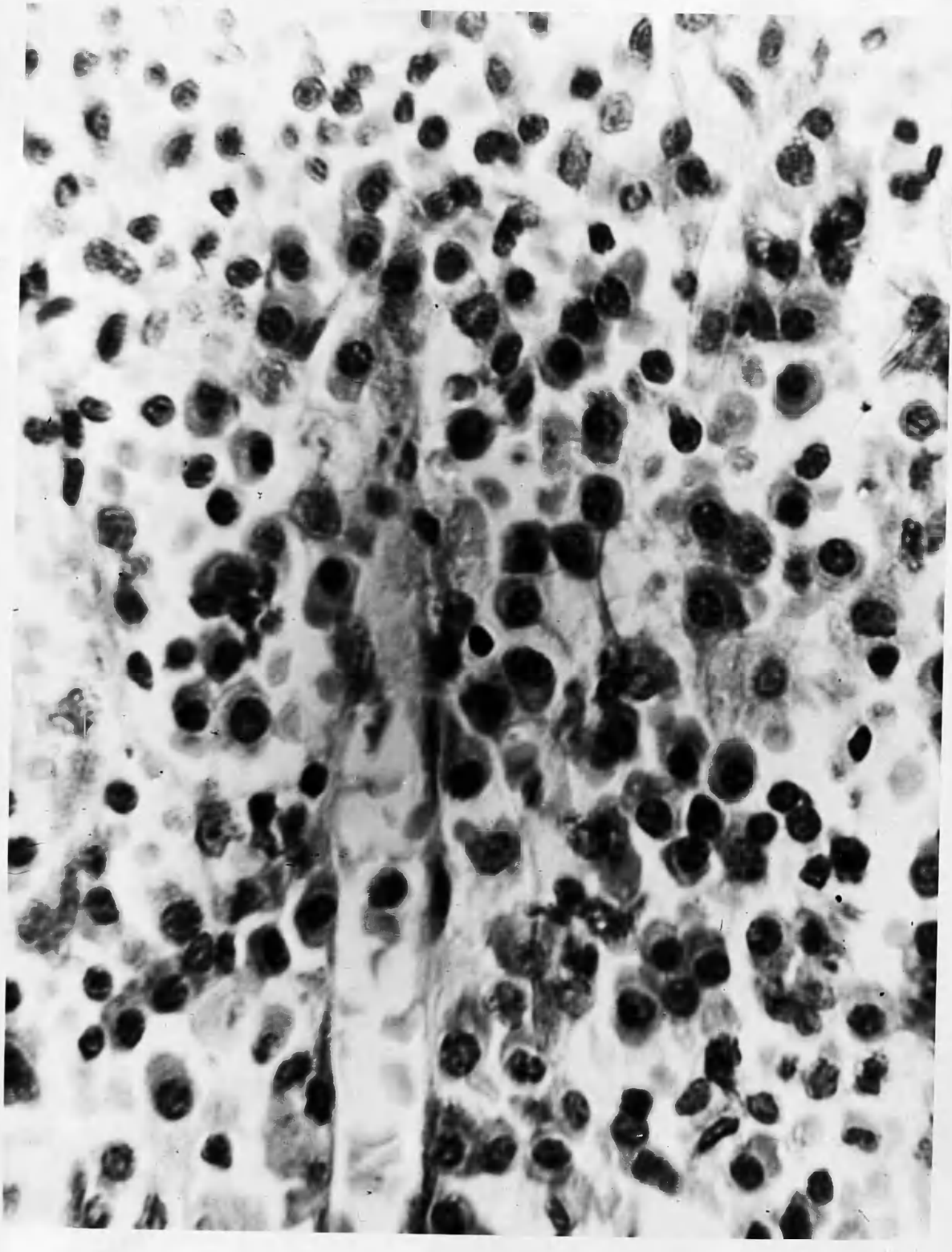
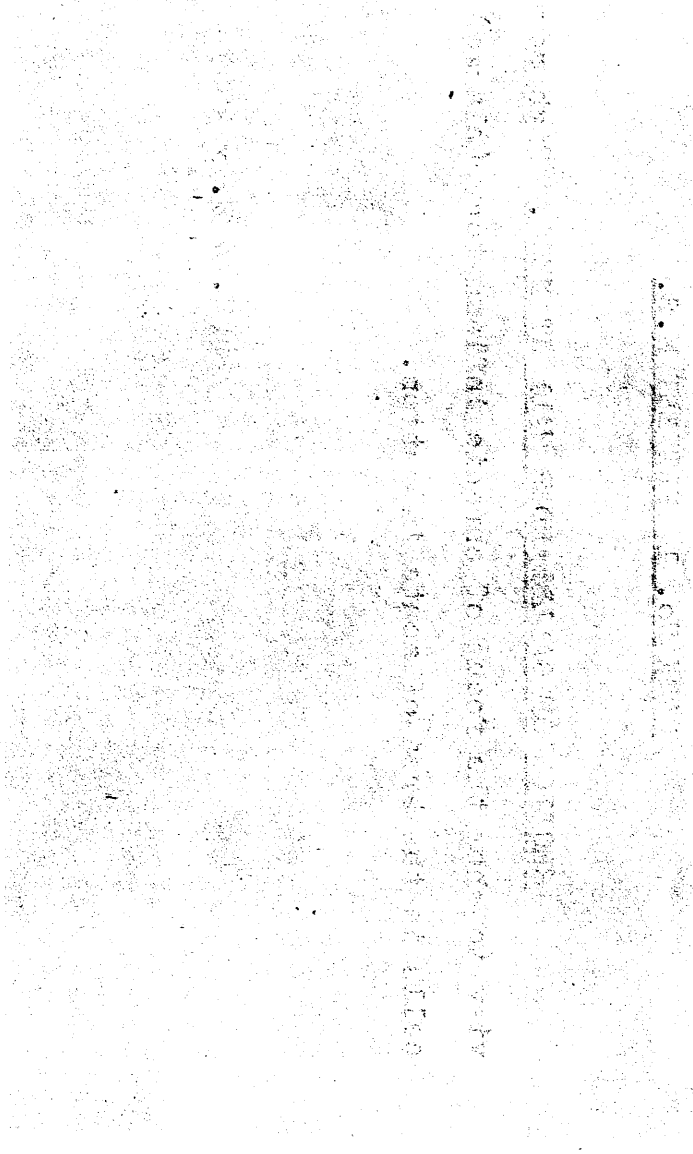


FIG. 43.

CASE No. 1 PATIENT M.S.

SECTION OF GALLBLADDER WALL AT NECK. High power view to show the focus of chronic inflammatory (plasma) cells in the area of acute infection.

(H. & E. x 300)



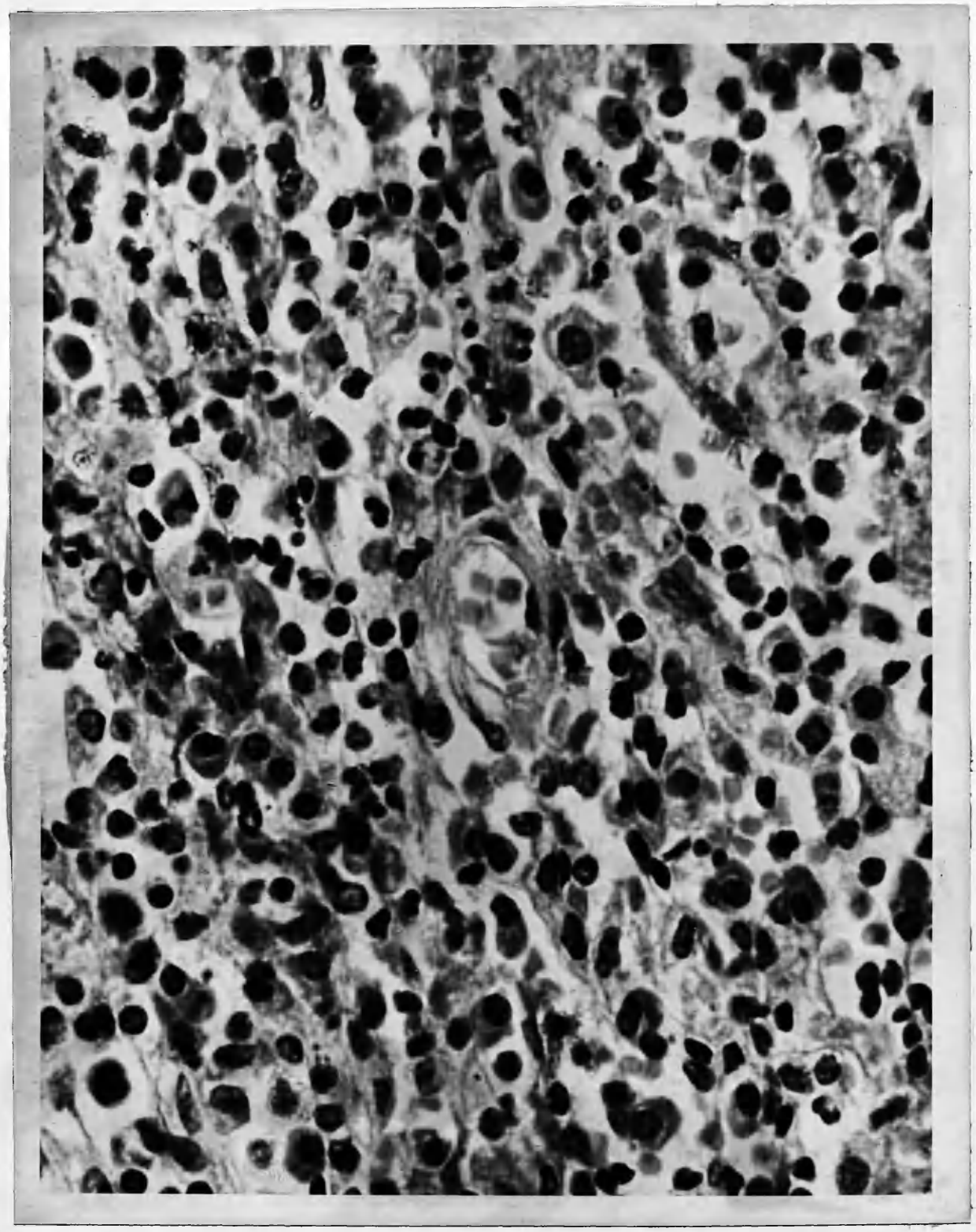


FIG. 44.

CASE No. 1 PATIENT M.S.

SECTION OF GALLBLADDER WALL AT NECK. High power view to show the predominantly polymorphic nature of the infiltrate. In addition small numbers of plasma cells are present. Vascularity is marked.

(H. & E. x 200)

FIG. 45.

CASE No. 2 PATIENT J.C.

SECTION OF GALLBLADDER WALL AT FUNDUS. The mucosa is thin and has been shed in places. There is diffuse infiltration of the mucosal remnant with inflammatory cells, with occasional denser foci. The inflammatory infiltration extends through the deeper layers which are fibrotic and show early fatty replacement.

Active chronic cholecystitis.

(H. & E. x 30)

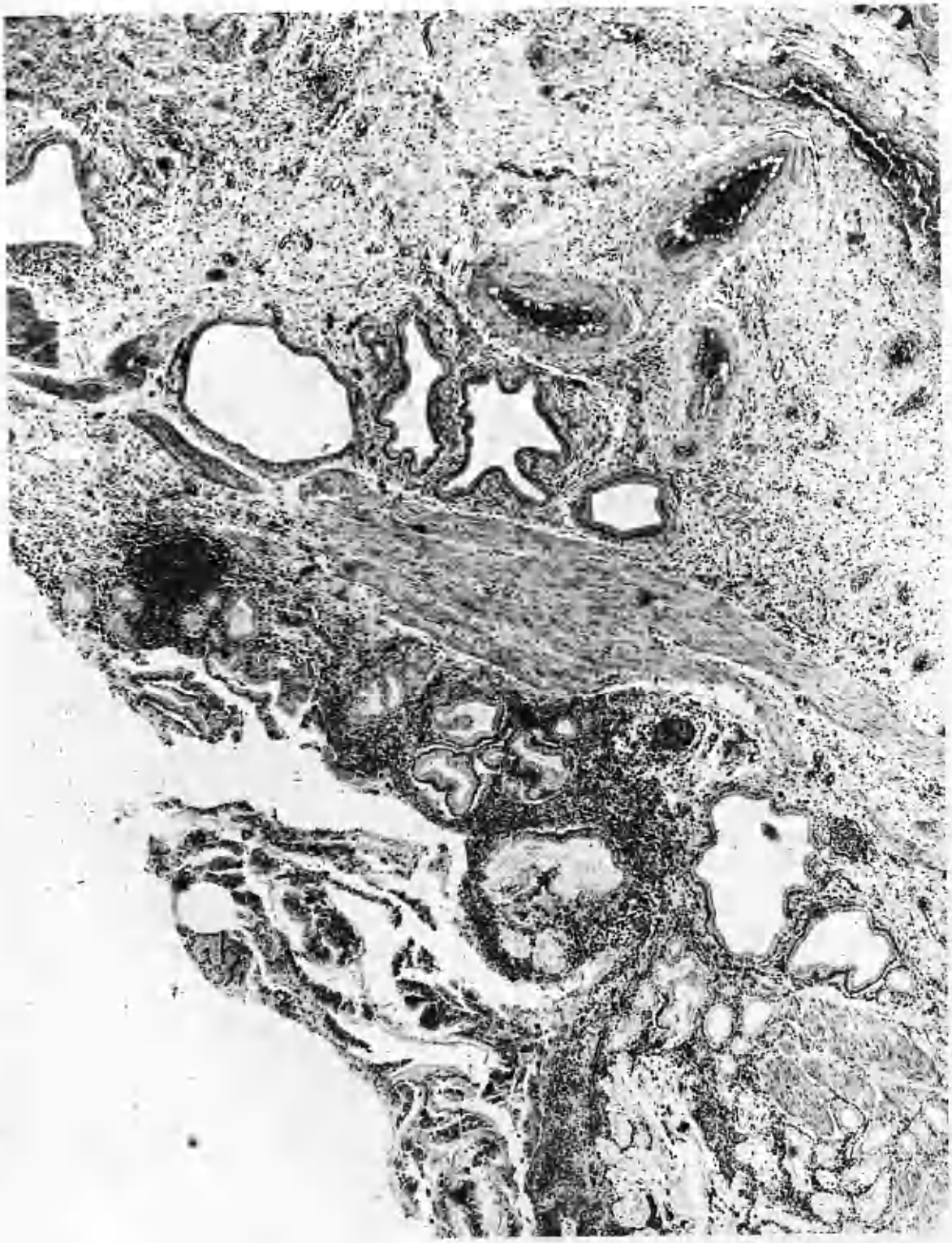


FIG. 46.

CASE No. 3 PATIENT J.K.

SECTION OF GALLBLADDER WALL AT FUNDUS. Dilated Rokitansky-Aschoff sinuses are well shown deep to the muscularis. There is a moderate diffuse inflammatory infiltrate of the mucosa proper and in the vicinity of the deep glandular extensions. A single "follicle" of inflammatory cells is present. Apart from slight oedema the muscularis is well preserved. Fibrosis is negligable.

Chronic cholecystitis.

(H. & E. x 50.)

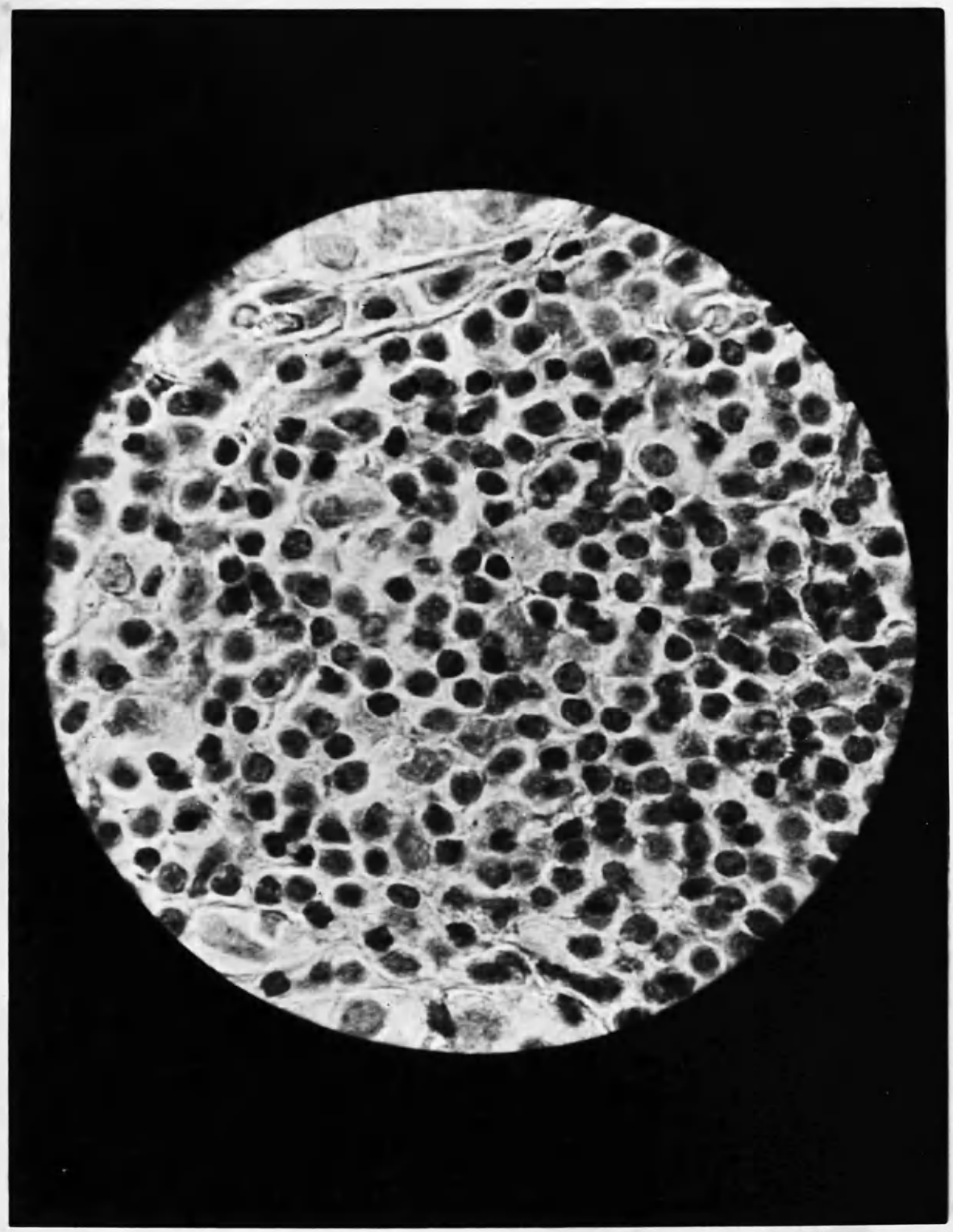


FIG. 47.

CASE No. 3 PATIENT J.K.

SECTION OF GALLBLADDER WALL AT FUNDUS. High power view to show centre of "follicle". (See Fig. 46.)
The cells are mainly mononuclear and lymphocytic.

(H. & E. x 200)

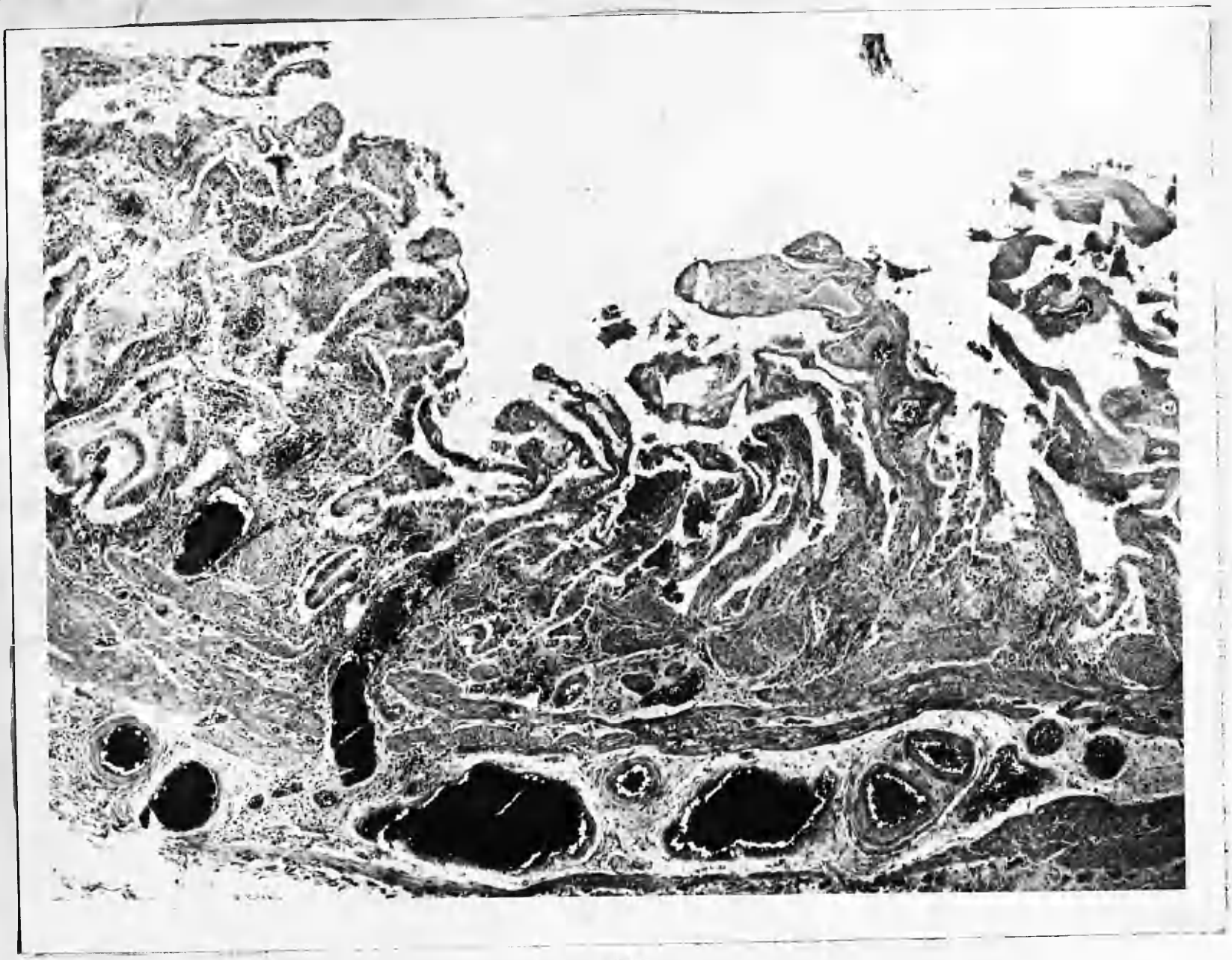


FIG. 48.

CASE No. 5 PATIENT D.S.

SECTION OF GALLBLADDER WALL AT FUNDUS. The mucosal thickness is normal but autolysis is extreme. There is sparse infiltration of the mucosa but marked engorgement of the local vessels. (See high power view fig. 49)

(H. & E. x 50)

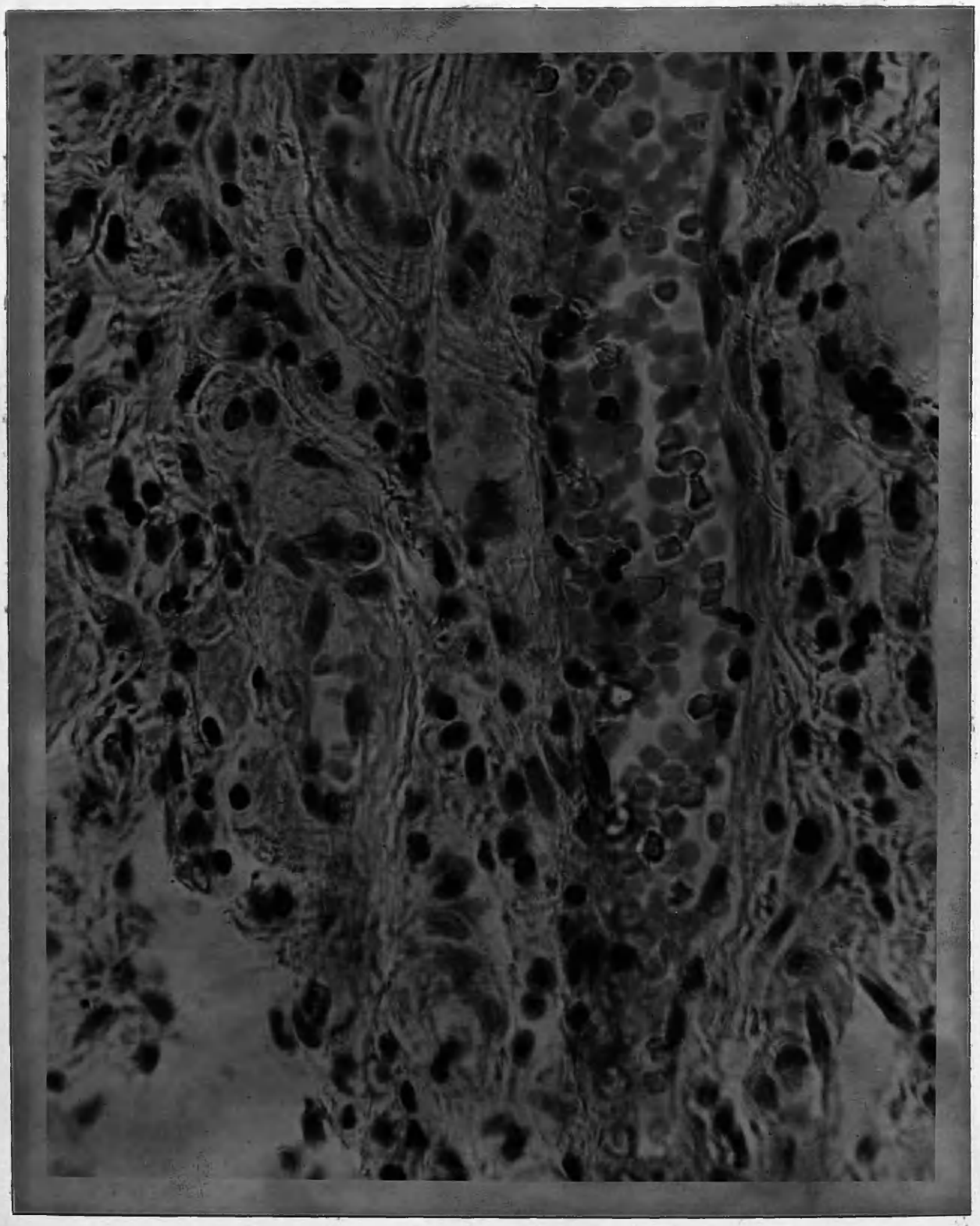
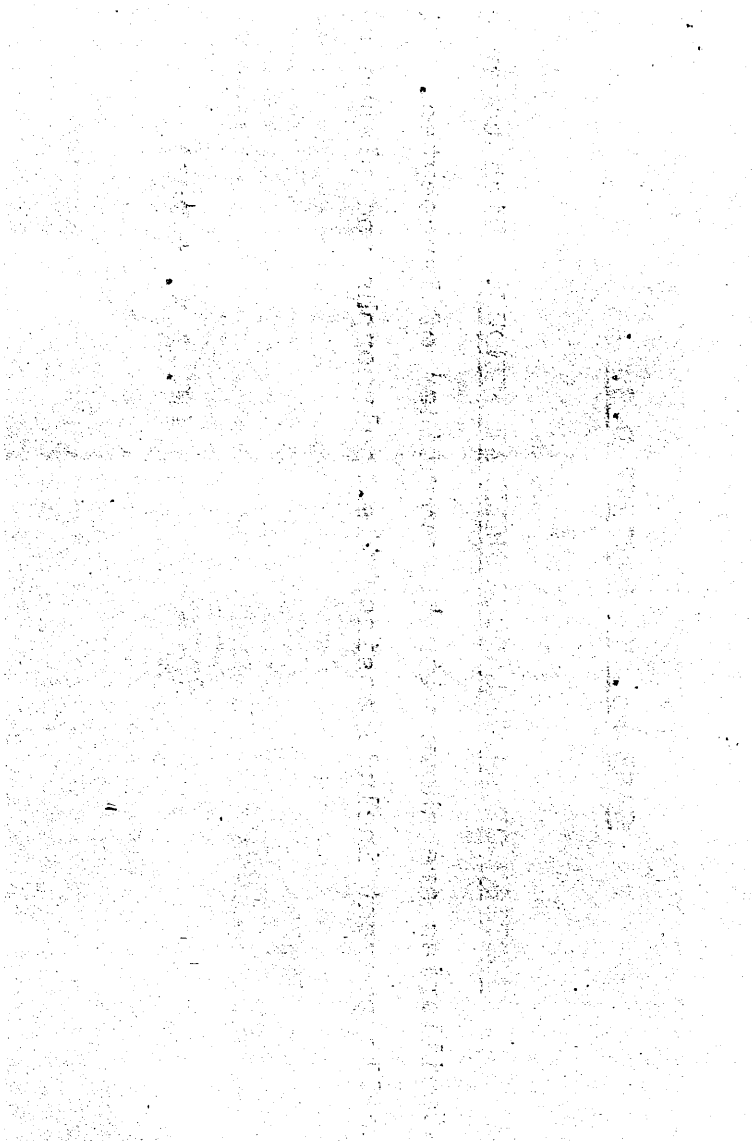


FIG. 49.

CASE No. 5 PATIENT D.S.

SECTION OF GALLBLADDER WALL AT FUNDUS. High power view. Capillaries are shown with "pavementing" of leucocytes. Other cells present include eosinophils, polymorphs and plasma cells.

(H. & E. x 200)



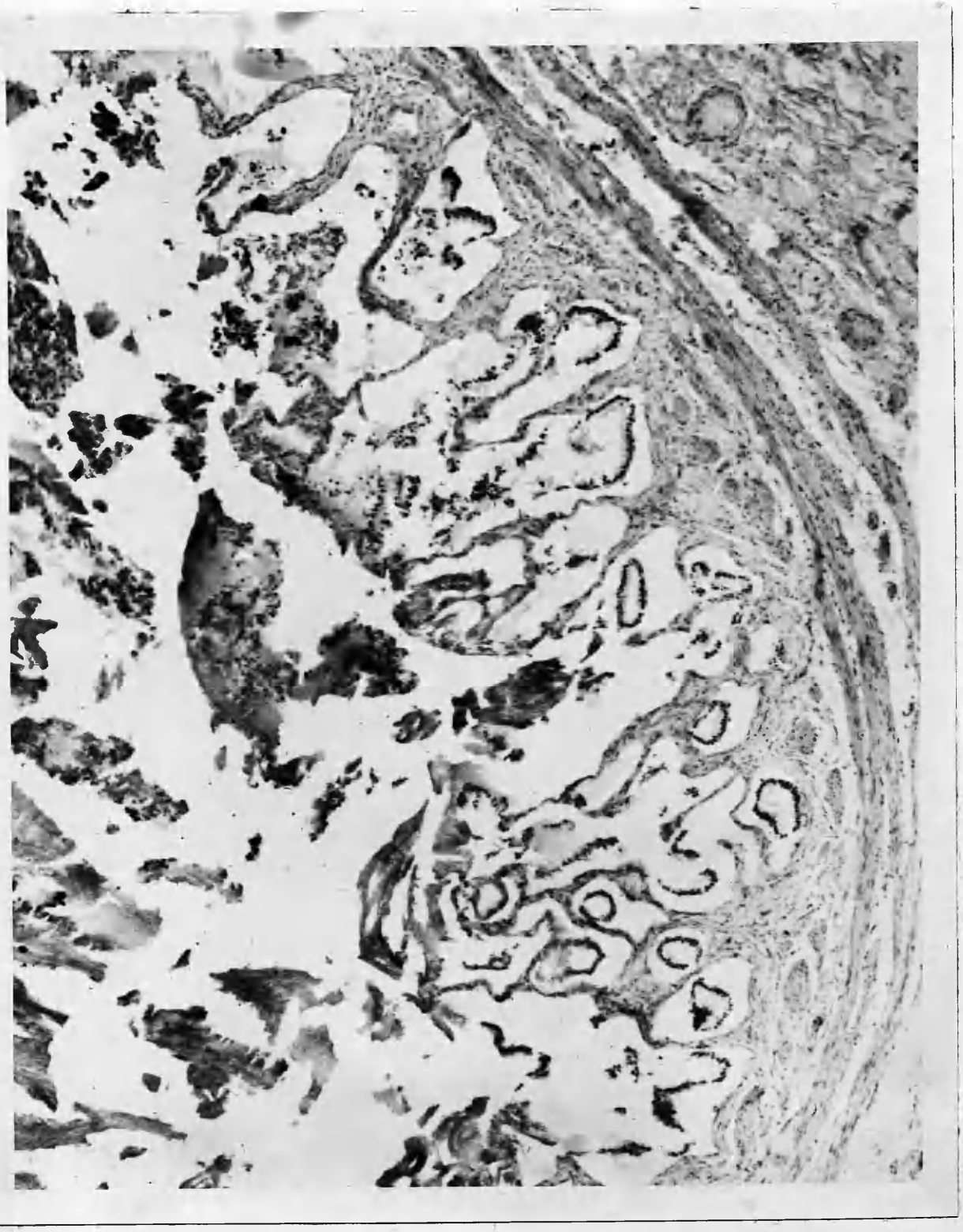


FIG. 50.

CASE No. 8 PATIENT H.McD.

SECTION OF GALLBLADDER WALL AT FUNDUS. The mucosal thickness is normal but autolysis is extreme. No appreciable inflammatory infiltrate is seen. The muscularis is thin but well preserved.

(H. & E. x 50)

The foregoing plates illustrate the detailed histological findings. A well-marked gradation is seen, the inflammatory changes being most marked in the most constant faecal excretors. There is round-cell infiltration which is most pronounced in the mucous coat. The "pseudo-follicles" noted by Browning and several other writers are well seen. This is a curious development which is difficult to explain. Perhaps these follicles represent a defence mechanism inserted by the body into the mucous coat of the gall-bladder in response to the enteric infection. The predominant cell is the plasma-cell. Next in order of frequency is the lymphocyte and occasional eosinophils are seen. The infiltrate appears to be extending deeply from the mucosaalong the tissue planes between the muscle bundles, suggesting the possibility that the infection is biliary in origin rather than a direct haematogenous spread to the gall-bladder.

It seems doubtful whether any antibiotic could justly be expected to eradicate this type of infection, even if it can reach the diseased gall-bladder in sufficient concentration.

S E C T I O N V11.

Post-operative observations.

- Monthly liver function tests.
- Monthly weights.
- Monthly blood sedimentation rates.
- Widal tests.

Detailed consideration of progress of case No. 2.

THE RESULTS OF POST-OPERATIVE LIVER FUNCTION TESTS.

SERUM BILIRUBIN.

CASE No.	PATIENT	E.F.[1]	PRE-OP	NOV '58	DEC '58	JAN '59	FEB '59	MAR. '59
1	M.S.	84	10·5[2]	0·4	0·2.	0·4.	0·3.	
2	J.C.	83	0·8	2·4	0·4.	2·0.	3·5.	
3	J.K.	53	1·0.	0·4	0·3	0·2.	0·4.	
4	H.McM.	33	0·8.	0·3	0·3.	0·4.	0·3.	
5	D.S.	23	0·8.	0·3	0·3	0·4.	0·2.	
6	J.Cr.	14	1·0.	0·2	0·2	0·2.	0·2.	
7	T.B.	10	0·2.	0·4	0·3	0·3.	0·2.	
8	H.McD.	10	0·2.	0·2	0·2	0·2	0·3.	
9.	W.F.	8.	0·2.	0·2	0·2	0·3.	0·3	

1. E.F. = EXCRETION FREQUENCY.
2. FIGURES IN MGMS/100 ML.

THYMOL TURBIDITY.

CASE No.	PATIENT	E.F.	PRE-OP.	NOV '58	DEC. '58	JAN '59	FEB. '59	MAR. '59
1	M.S.	84	7.[1]	2.	2.	2.	3.	
2	J.C.	83	3.	3.	2.	1.	2.	
3	J.K.	53	2.	1.	1.	2.	2.	
4	H.McM.	33	2.	1.	1.	1.	2.	
5	D.S.	23	4.	1.	1.	1.	3.	
6	J.Cr.	14	2.	1.	2.	1.	2.	
7	T.B.	10	3.	2.	2.	2.	5.	
8	H.McD.	10	—	2.	1.	1.	3.	
9.	W.F.	8	1.	1.	2.	2.	3.	

1. FIGURES IN UNITS.

SERUM ALKALINE PHOSPHATASE.

CASE No.	PATIENT	E.F.	PRE-OP.	NOV '58	DEC. '58	JAN '59	FEB. '59	MAR. '59.
1	M.S.	84	32.[1]	6.	7.	6.	5.	
2	J.C.	83	8.	9.	7.	7.	7.	
3	J.K.	53	6.	6.	7.	6.	5.	
4	H.McM.	33	6.	5.	7.	7.	6.	
5	D.S.	23	5.	7.	7.	6	7.	
6	J.Cr.	14	12.	6	8.	7.	8.	
7	T.B.	10	7.	7.	8	8.	9.	
8	H.McD.	10	9.	5.	6.	6.	6.	
9.	W.F.	8	6.	7	8.	8.	6·4.	

1. FIGURES IN KING & ARMSTRONG UNITS.

THE RESULTS OF POST-OPERATIVE LIVER FUNCTION TESTS.

(continued.)

TOTAL PLASMA PROTEINS.

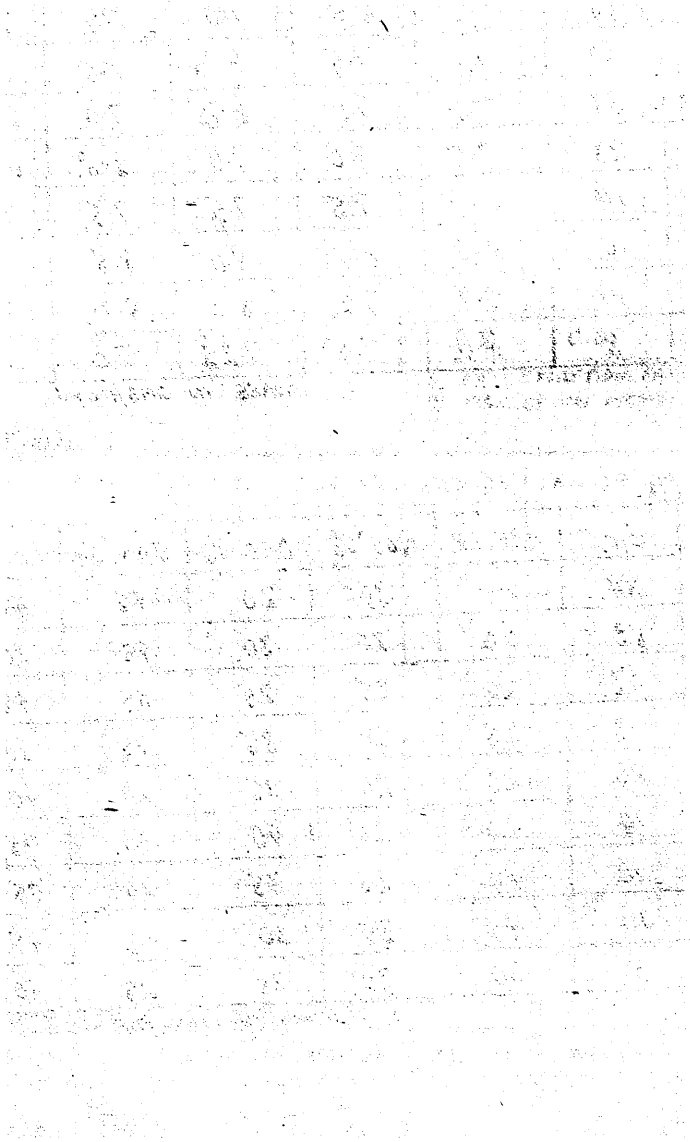
CASE Nº	PATIENT	E.F.	PRE-OP.	NOV '58	DEC. '58	JAN '59	FEB. '59	MAR. '59.
1.	M.S.	84.	7.0'	7.0	7.0.	7.25.	7.25.	
2.	J.C.	83.	7.0	6.5	7.0	7.5.	7.5.	
3.	J.K.	53.	7.0	7.5	6.75	7.5.	6.5.	
4.	H.McM.	33.	7.0	7.0	6.75	7.0.	6.75.	
5.	D.S.	23.	7.5.	8.0	7.0	8.5.	6.75.	
6.	J.Cy	14.	6.75.	7.5	7.5	7.5.	7.0.	
7.	T.B.	10.	8.5.	8.25	8.0.	8.5.	7.75.	
8.	H.McD.	10.	8.0.	7.75	8.0.	8.25.	7.0	
9.	W.F.	8.	8.0.	7.5	7.25.	7.0.	7.5.	

1. FIGURES IN GMS/100ml.

BLOOD UREA.

CASE Nº	PATIENT	E.F.	PRE-OP.	NOV. '58	DEC '58	JAN. '59	FEB. '59	MAR. '59.
1.	M.S.	84.	—	30.	20.	45.	40.	
2.	J.C.	83.	20'	20	30.	40.	20.	
3.	J.K.	53.	20	25	25.	35.	45.	
4	H.McM.	33	25	30	35	35.	30.	
5.	D.S.	23	20	20	35	20.	40.	
6.	J.Gy.	14.	20	25.	40.	30.	45.	
7.	T.B.	10.	40.	25	35	20.	35.	
8.	H.McD.	10.	40	35	30.	45.	45.	
9.	W.F.	8.	30.	30	30.	25.	40.	

1. FIGURES IN MGMS/100 ml.



COMMENT.

From a study of the monthly serum bilirubin chart, it will be seen that in eight of the carriers the level fell to or remained at 0.4 mgms. or lower. In Case No. 2, however, there was a persistently high reading. This was later found to be of significance. It was of interest that while the bilirubin level in this case remained high, there was no accompanying rise in thymol turbidity or serum alkaline phosphatase. A positive stool culture was found in this patient in February, 1959.

CONCLUSIONS.

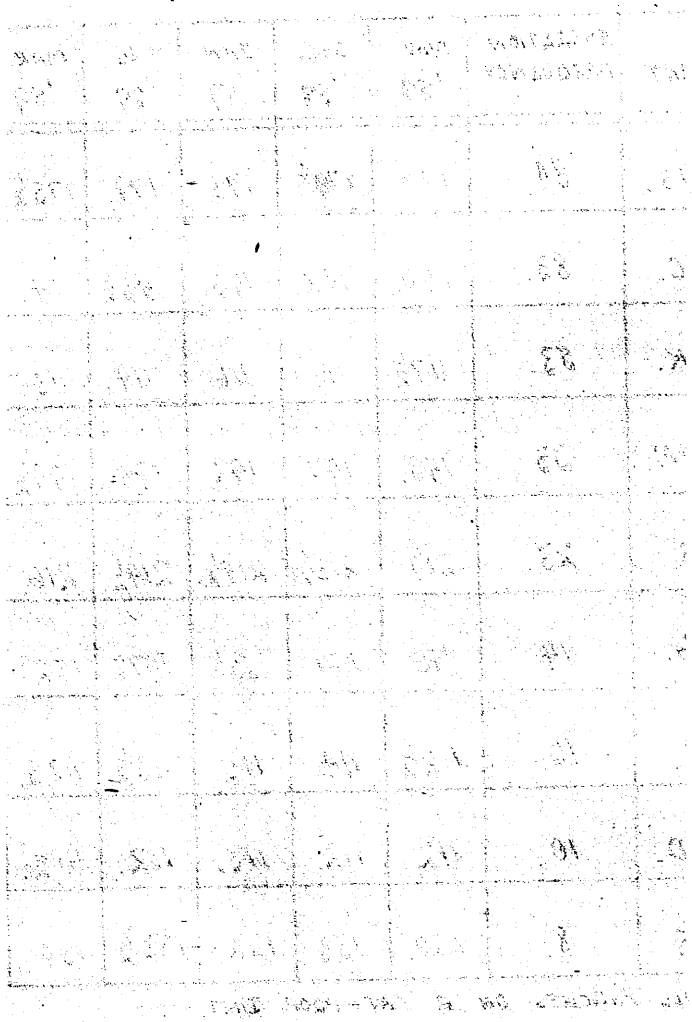
1. Cholecystectomy in the chronic enteric carrier causes a reversion to normal of the serum bilirubin level in those cases in which it is slightly elevated.

2. A persistently high serum bilirubin after cholecystectomy suggests the possibility of continued ductal infection.

TABULATED MONTHLY WEIGHTS IN POUNDS OF THE NINE CARRIERS OVER THE POST-OPERATIVE PERIOD.

CASE Nº	PATIENT	EXCRETION FREQUENCY	NOV '58	DEC. '58	JAN '59	FEB. '59	MAR. '59
1.	M.S.	84.	177.	179½.	178.	179.	175½.
2.	J.C.	83.	140.	142.	143.	143½	134.
3.	J.K.	53.	117½	118.	116.	114.	115.
4.	H.McM.	33.	148.	147.	148.	148.	149½.
5.	D.S.	23.	217	215½	214½.	214½.	216.
6.	J.Cy.	14.	146	150	150½	147½.	152.
7.	T.B.	10.	112½	114.	113.	113½.	112½.
8.	H. McD.	10.	112.	112.	113.	112.	111½.
9.	W.F.	8.	154.	153.	153.	153½.	154.

ALL PATIENTS ON A FAT-POOR DIET.



TABULATED MONTHLY BLOOD SEDIMENTATION RATES OF THE NINE CARRIERS OVER THE POST-OPERATIVE PERIOD.

CASE Nº	PATIENT.	EXCRETION FREQUENCY	NOV '58	DEC. '58	JAN '59	FEB. '59	MAR '59.
1.	M.S.	84.	13 / 35	7 / 18	3 / 9	10 / 20	3. / 6.
2.	J.C.	83.	27 / 56	25 / 32	18 / 43	30 / 48.	47. / 84.
3.	J.K.	53.	25 / 58	29 / 57	26 / 55	35 / 68	16. / 34.
4.	H.M'M.	33.	3 / 8	4 / 10	28 / 31	7 / 13	3. / 6.
5.	D.S.	23.	7 / 23	3 / 6	5 / 8	5 / 10	4. / 11.
6.	J.Cr.	14.	3 / 8	7 / 16	7 / 16	4 / 15	3. / 5.
7.	T.B.	10.	5 / 15	3 / 5	2 / 8	3 / 5	5. / 7.
8.	H.M'D.	10.	4 / 13	9 / 17	5 / 20	8 / 15	5. / 9.
9.	W.F.	8.	9 / 32	8 / 20	8 / 15	9 / 22.	2. / 3.

mms in 1st hour
mms in 2nd hour

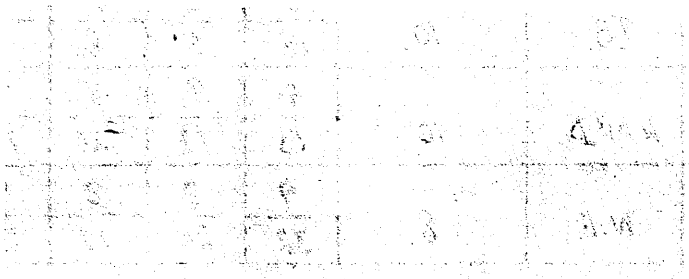
The sedimentation rates were estimated by the Westergren method. Cases 2 and 3 showed persistently high readings post-operatively. Case 3, however, was found to have a haemoglobin of 74%. His blood sedimentation rate was therefore estimated by the Wintrobe method so that suitable correction could be made. When this was done there appeared to be no really significant elevation.

His albumen/globulin ratio and electrophoretic pattern were also checked and found to be normal. (V. also p. 31 – chest X-ray).

Case 2 was the patient who produced a positive stool culture during February 1959 and whose serum bilirubin remained elevated.

CONCLUSION.

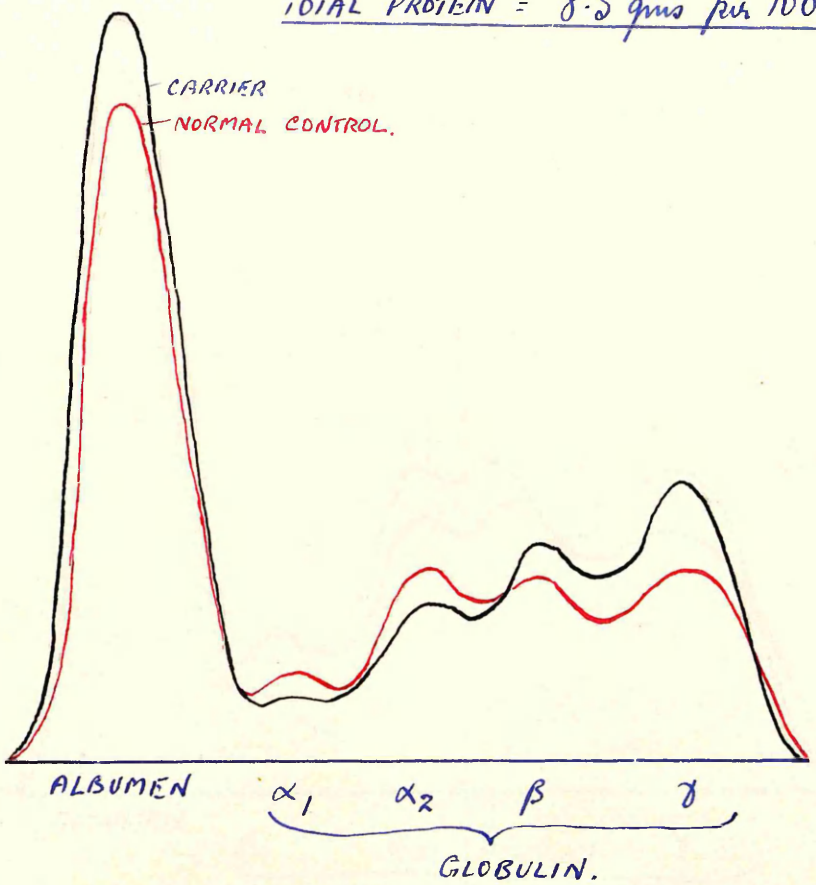
The blood sedimentation rate is of some help in tracing the carrier who does not make an immediate response to cholecystectomy.

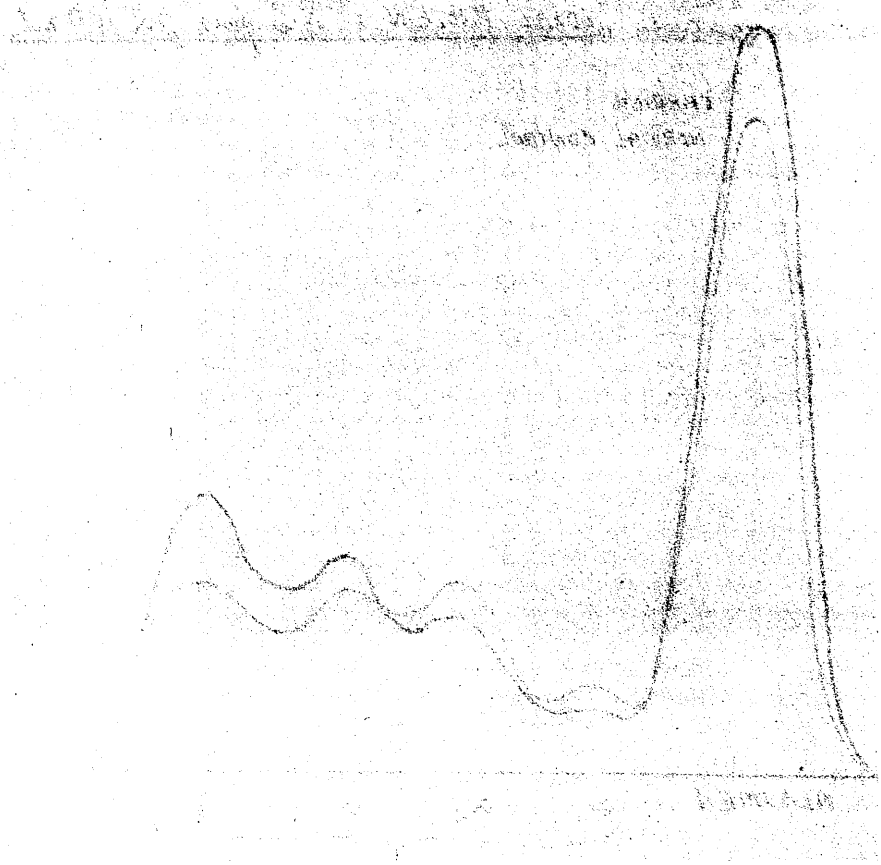


ELECTROPHORETIC PATTERN

CASE No 3. PATIENT J.K.

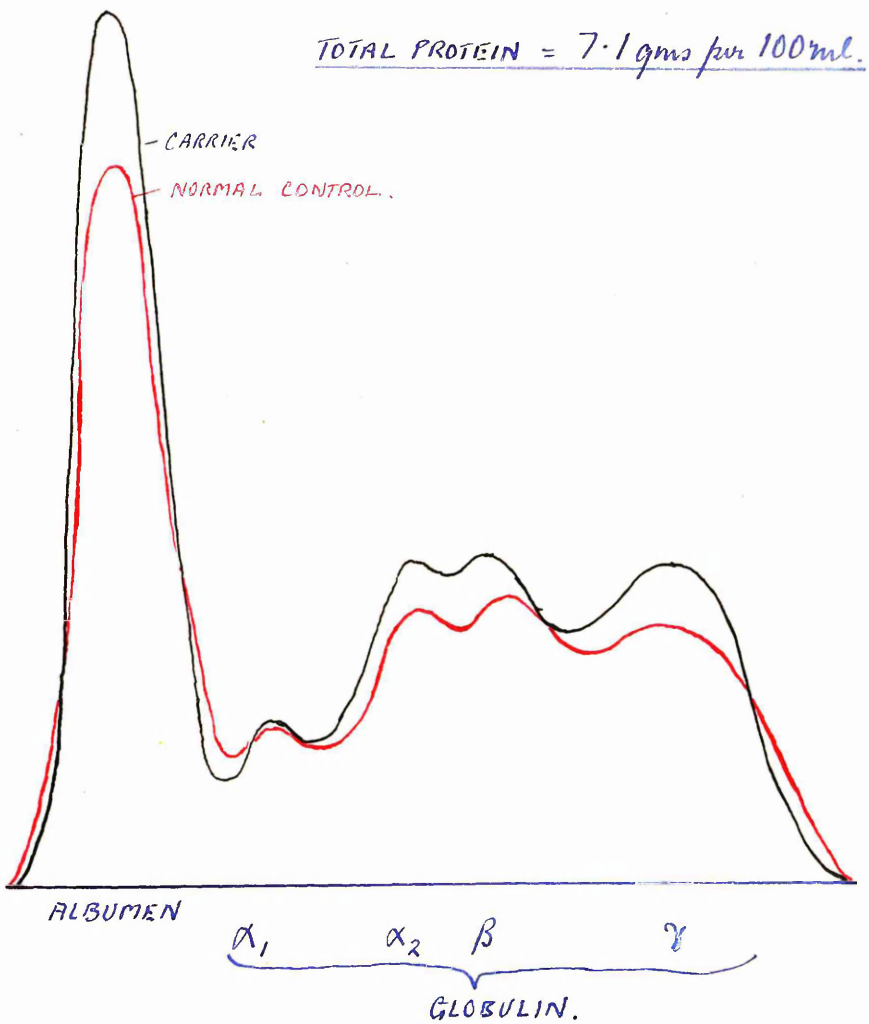
TOTAL PROTEIN = 8·3 gms per 100 ml.

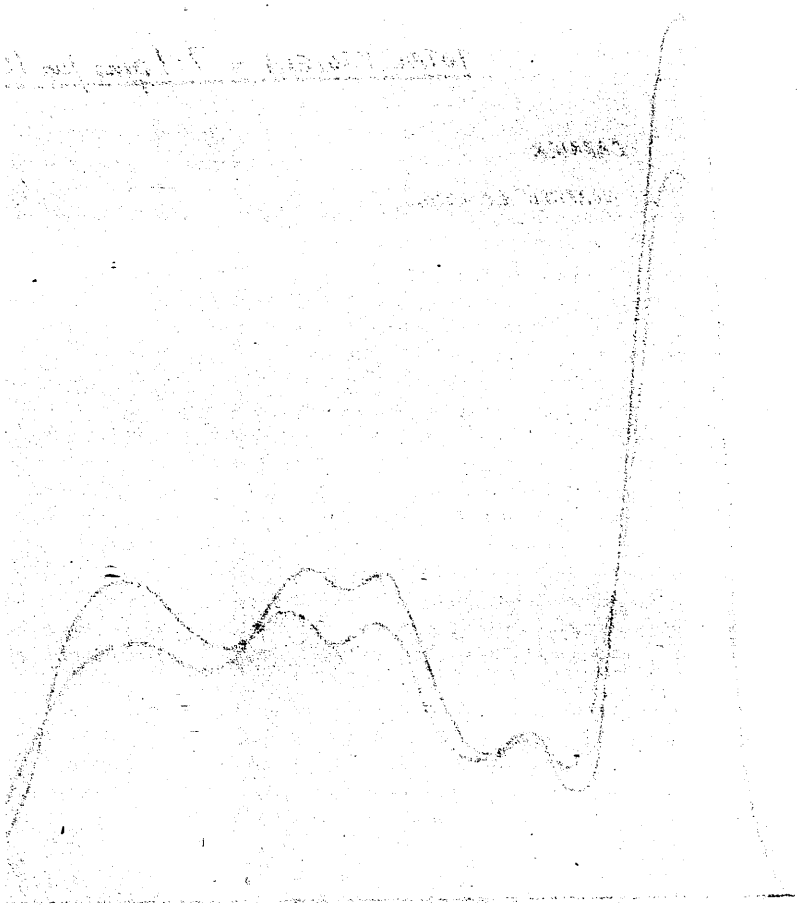




ELECTROPHORETIC PATTERN

CASE Nº 2. PATIENT J.C.





THE WIDAL REACTION.

Kayser (1929) stated that 75% of carriers reacted positively.

Haaland (1920) found a negative reaction not infrequently in healthy carriers. He stated that a positive Widal reaction meant a positive persistent chronic infection and not merely a saprophytic existence. (It may be doubted whether such a saprophytic state really exists. Author.)

Browning et al. (1933) stated that while the rise and fall in agglutininsfor S. typhi and S. paratyphi A. and B. are found to occur simultaneously when the same carriers serum is tested repeatedly, nevertheless at times the agglutinating action of heterologus organisms (e.g. S. paratyphi A. in a carrier of S. typhi) may be much more marked than that on the homologous organism. (This would appear to be in accord with the results in the present series.)

Browning et al. had no satisfactory explanation for the co-agglutination which occurs in acute enteric infections.

There follows a detailed record of serial Widal tests.

Record of serial Widal Tests.

CASE Nº 1. M.S.

		NOV. '58.	DEC. '58	JAN '59.	FEB. '59	MAR. '59.
B. TYPH. O.		–	–	–	–	–
" " H.		–	–	–	–	–
" " Vi.		–	–	–	–	–
S. PARA A. O.		–	–			
" " " H.		–	–			
S. PARA B. O		–	–	–	–	–
" " " H.		1/100	1/250.	1/100.	1/500.	1/500

CASE Nº 2. J.C.

	SEP. '57.	NOV. '58	DEC '58	JAN. '59	FEB. '59	MAR. '59.
B. TYPH. O	–	–	–	–	–	–
" " H.	–	–	–	–	–	–
" " Vi	1/10	–	–	–	–	–
S. PARA A O	–	–	–			
" " " H.	–	–	–			
S. PARA. B. O	–	–	1/50	1/25.	1/25.	–*
" " " H.	1/1000.	–	1/250.	1/250.	1/500.	1/250.

RE-OPERATION.

CASE Nº 3. J.K.

	AUG. '57.	NOV '58	DEC. '58	JAN, '59	FEB '59	MAR '59.
S. TYPH. O.	–	–	–	–	–	–
" " H.	–	–	–	–	–	–
" " Vi.			–	–	–	–
S. PARA A O.		–	–			
" " " H.		1/50.	–			
S. PARA B O.	1/50.	–	–	–	–	–
" " " H.	1/250.	–	1/125.	1/50.	1/50.	–

CASE Nº 4. H.McM.

	SEP. '57	NOV. '58	DEC. '58.	JAN. '59.	FEB. '59	MAR. '59.
S. TYPH. O.	–	–	–	–	–	–
" " H.	1/50.	1/25.	–	–	–	–
" " Vi.	1/40.	–	–	–	–	–
S. PARA A. O.	–	–	–			
" " " H.	–	–	–			
S. PARA B. O.	–	–	–	–	–	–
" " " H.	–	1/25.	–	–	–	–

CASE Nº 5. D.S.

	AUG. '57	NOV. '58	DEC. '58.	JAN. '59	FEB. '59	MAR. '59.
S. TYPH. O	1/50	–	–	–	–	–
" " H.	–	–	–	–	–	–
" " Vi.			–	–	–	–
S. PARA A O		–	–			
" " " H.		–	–			
S. PARA B O	1/50.	–	–	–	–	–
" " " H.	1/250.	1/50.	1/250.	1/200.	1/250.	1/250.

CASE Nº 6. J.Cy.

	SEP. '57	NOV. '58	DEC. '58.	JAN. '59	FEB. '59	MAR. '59.
S. TYPH. O.	–	–	–	–	–	–
" " H.	1/50.	1/100.	–	1/50	–	–
" " Vi.	–	–	–	–	–	–
S. PARA. A. O	–	–	–			
" " " H.	–	1/50.	–			
S. PARA. B. O.	–	–	–	–	–	–
" " " H.	1/25.	–	1/250	1/100.	1/100.	1/250

CASE. Nº 7. T.B.

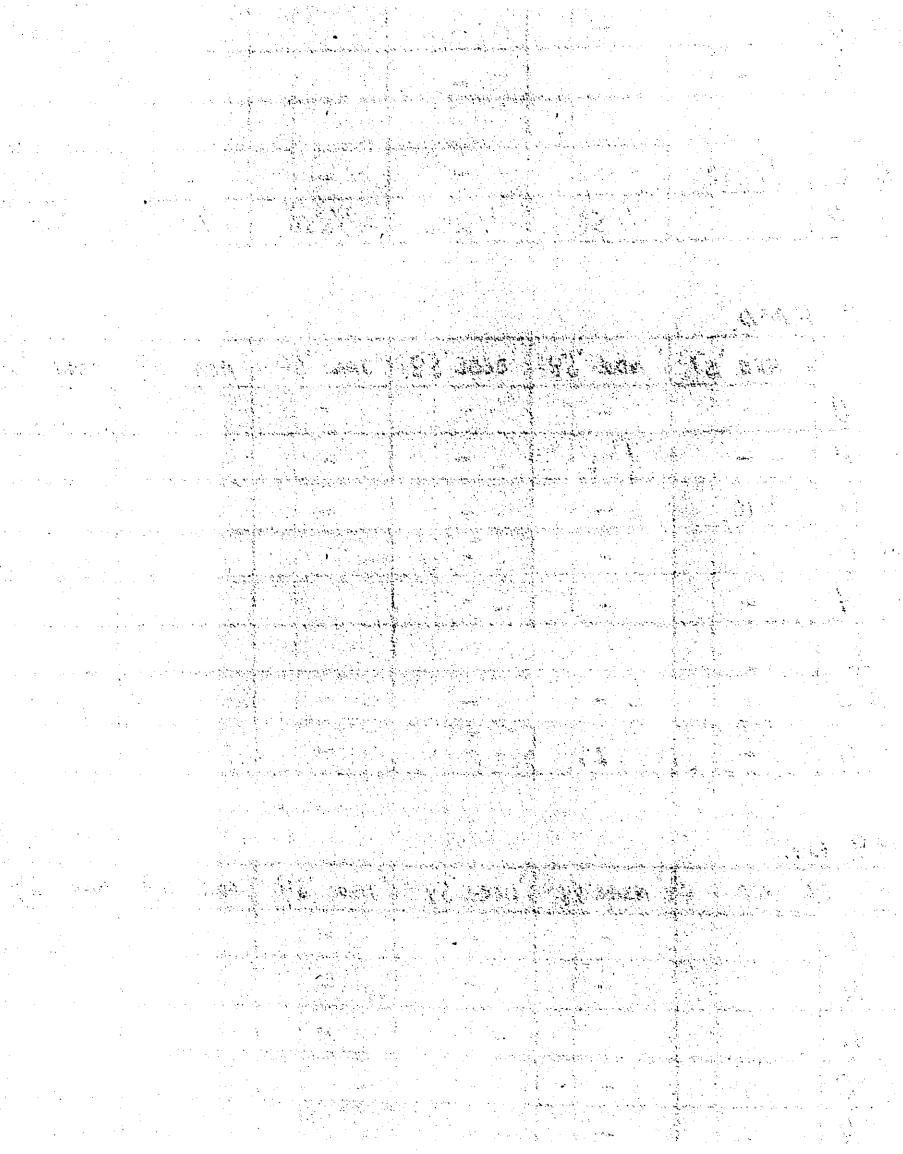
	JUL. '51.	NOV. '58	DEC. '58.	JAN. '59	FEB. '59	MAR. '59.
S. TYPH. O.	1/2500.	–	–	–	–	–
" " H.	1/2,500.	–	–	–	–	–
" " Vi.	–		–	–	–	–
S. PARA A. O	–	–	–			
" " " H.	–	–	–			
S. PARA B. O.	1/250.	–	–	–	–	–
" " " H.	–	1/50.	1/250.	1/250.	1/100.	1/250

CASE. Nº 8. H.McD.

	AUG. '51.	NOV. '58	DEC. '58	JAN. '59	FEB. '59	MAR '59.
S. TYPH. O.	–	–	–	–	–	–
" " H.	–	1/25	–	–	–	–
" " Vi.	1/10.	–	–	–	–	–
S. PARA A O	–	–	–			
" " " H.	–	–	–			
S. PARA B O	–	–	–	–	–	–
" " " H.	–	1/25.	–	–	–	–

CASE. Nº 9. W.F.

		NOV. '58	DEC. '58	JAN. '59	FEB. '59	MAR. '59.
S. TYPH. O.		–	–	–	–	–
" " H.		–	–	–	–	–
" " Vi.			–	–	–	–
S. PARA. A. O		–	–			
" " " H.		–	–			
S. PARA B. O.		–	–	–	–	–
" " " H.		1/25.	–	1/25.	–	–



From the tables it is seen that the results of the tests are variable and can only be interpreted broadly.

COMMENTS.

1. The phenomenon of co-agglutination is seen.

2. A positive "H" titre tends to remain after cholecystectomy.

3. In only one case - Case 2 - was a positive "O" titre found post-operatively and it was persistent. This was the patient who showed a positive stool in February, 1959.

DETAILED POST-OPERATIVE CONSIDERATION OF CASE No. 2.

PATIENT J.C.

This patient was one of the two most constant pre-operative excretors. After cholecystectomy, although the stool cultures were negative for four consecutive months his progress was observed with some concern. In the first place he was noted from time to time to have a faint icteric tinge in the conjunctivae (although he seemed perfectly well and gained slightly in weight).

The monthly serum bilirubin figures were as follows:-

Nov. 58	Dec. 58	Jan. 59	Feb. 59.
2.4	0.4	2.0	3.5

mgms. per 100 ml.

In the initial post-operative stages, bearing in mind that in this patient it was felt necessary to drain the dilated common bile-duct, a suspicion was entertained that the rising bilirubin might be associated with common duct scarring. That the cause of the rising bilirubin was extra-hepatic in situation was suggested by the fact that liver function tests simultaneously showed progressive improvement. White cell count remained normal.

	Nov. 58	Dec. 58	Jan. 59
Thymol turbidity. (units.)	3	2	1
Serum alk. phosph. (K & A units)	9	7	7
Serum proteins (gm./100 ml.)	6.5	7	7.5

Nevertheless the result of monthly Widal tests showed that this was the only patient of the nine who showed post-operative agglutination to S. paratyphi B. "O" as well as "H", and this suggested that the cause of the rising serum bilirubin was in fact a persistent cholangitis. This contention was supported by the fact that the blood sedimentation rate remained persistently high in face of a normal haemoglobin and electrophoretic pattern. A recurrence of faecal excretion of the organisms

was expected monthly and, in fact, a positive stool culture was obtained in February 1959.

When this event arose he was isolated in the Ward as far as possible and a course of oral neomycin instituted to try to prevent spread of the infection.

On 8th February 1959, intra-venous cholangiography was performed to see whether there was evidence of stone or stasis in the common duct. No sign of stone was found but there seemed to be definite delay in excretion. At 100 minutes after the injection the duct was well outlined. It was somewhat dilated and showed a normal contour with no evidence of scarring. The dye had still not entered the duodenum.

Arrangements were therefore made for further operative intervention with a view to

a) establishing further drainage by "T"-tube.
b) using this route for the introduction of neomycin solution.
c) establishing and if possible eliminating the cause of the biliary stasis.

Theatre. 12.2.59. Mr. Main. Anaesthesia. Dr. Beaton. Thiopentone, Nitrous oxide, Oxygen, Fluothane, Flaxedil.

A right, epigastric, vertical, rectus-splitting incision was made. lateral to the former incision. Omental adhesions were dissected and the common bile-duct was exposed. It was somewhat dilated and its wall was thickened. Choledochotomy was performed and the interior of the duct inspected. The lining was very vascular. Both hepatic ducts were probed. No stones were found and both seemed quite patent. On probing distally again no stones were encountered but two small firm fibrinous plaques were removed. A fine bougie was passed into duodenum after some initial resistance. The anterior wall of the duodenum was then incised longitudinally and the ampulla of Vater was defined. Thereafter dilatation was carried out, using graduated bougies and the choledochal sphincter was divided under direct vision over the largest bougie. A "T"-tube was next inserted into the common bile-duct and the duct closed. The duodenal incision was then closed transversely, using two continuous catgut sutures. A Penrose drain was left in the upper end of the abdominal wound. The bile was golden brown and not at all turbid.

The appendix was inspected and although it did not appear inflamed, was unusually large, measuring 7.5 cms. long by 2 cms. across the base. It was removed.

The abdominal incision was then closed in layers.

The following specimens were kept for examination.

1. Bile for culture and assay.

2. Part of appendix and contained inspissated faeces for culture.

3. Main body of appendix for histology.

Convalescence following this operation was uneventful. The serum bilirubin rose initially to 7.5 mgms. per 100 ml. but fell in one week to 2.25 mgms. per 100 ml. and is still falling.

It is hoped to drain the common bile-duct for a period of six weeks assuming negative cultures of enteric organisms and during this time the following program is proposed:-

1. The bile will be cultured daily.. So far no enteric organisms have been isolated and difficulty is being experienced because of overgrowth of b. coli and enterococci.

2. Single large doses of those antibiotics to which the organism was found to be sensitive will be administered orally and then parenterally and three hours later bile specimens will be examined for antibiotic content.

3. When this investigation is complete daily injections of neomycin solution will be made into the "T"-tube.

4. Before removal of the tube, a cholangiogram will be made to confirm patency of the common-duct orifice.

Note. The appendix and its contained faeces failed to yield a positive culture of enteric organisms.

The oral neomycin therapy ceased on 23.2.59.

Histological examination of the appendix showed evidence of mild previous inflammation but otherwise the organ was not remarkably abnormal and no specific changes could be found.

The ultimate outcome of this case is awaited with considerable interest.

S E C T I O N V111.

Discussion and general conclusions.

The problem in Scotland.

The problem abroad.

DISCUSSION AND GENERAL CONCLUSIONS.

It is now more than half a century since it was first realised that chronic carriers played a part in the dissemination of enteric fever. A study of the role of the gall-bladder and biliary tract over the years has led to the gradual realisation of its importance in relation to biliary carriers. It is contended that the studies carried out in the present work establish beyond reasonable doubt, its culpability in the alimentary carrier. For the first time, carriers have been graded according to their excretion frequency and it has been shown that the frequency of excretion is directly related to the loss of function and degree of pathological change in this organ. In eight alimentary carriers in a Mental Institution the removal of the gall-bladder has led to the elimination of the carrier state and a cessation of faecal excretion of the organisms. This has been accompanied by an improved liver function, improved general health, psychological uplift and the prospect of free social intercourse and the opportunity for group therapy, definitive psychiatric treatment and rehabilitation. These results have been accomplished without mortality or morbidity. The outcome of a 9th case is still sub judice.

The surgical treatment of the carriers was supplemented by antibiotic therapy with neomycin. It seems likely that this agent played only a subsidiary part in achieving the results and that it reduced the period of post-operative excretion.

From the investigation, several interesting observations are suggested.

1. Route of infection.

The infection seems to be maximal at the mucosal side of the gall-bladder wall on histological examination as judged by the inflammatory reaction. This is taken as indicating that the gall-bladder is infected via the bile.

2. The gall-bladder lesion.

Although Garbat's "test-tube" theory may be, and probably is, correct, there is in the series a quite definite correlation as noted above, between the excretion

frequency and the degree of pathological change in the gall-bladder wall.

3. The ducts.

It is interesting that in Case No. 2 (Patient J.C.), there was an indication of some persistent activity in the ducts and that, althoughthe stools remained negative for a period of four months after operation, a rising serum bilirubin was followed by a positive stool at the fifth month. This, it is to be noted, was a patient in whom at the original operation there was evidence of stasis in the common bile-duct and it seems likely therefore that biliary stasis favours continued infection, even after the cul-de-sac of the gall-bladder has been removed.

4. Extra-hepatic and extra-biliary foci.

There is no evidence of persistence of infection in any other site in any of the nine carriers and no evidence to support Badia's contention that the longer the duration of the carrier state the more likely is the infection to have progressed to the ducts and liver.

5. The true intestinal carrier.

There is no evidence in the findings to support the view that the true intestinal carrier exists.

6. Gall-stones - post hoc or propter hoc?

The absence of gall-stones is not a contra-indication to operative treatment. There has in the past been much argument as to whether patients become chronic carriers more readily if their gall-bladders contain stones or whether stones arise as the result of continued chronic enteric cholecystitis. The fact that the patient M.S. had a high excretion frequency and advanced histological changes indicates that a high excretion frequency can occur in a chronic carrier of long-standing without stones. The argument seems to the writer fruitless and to have no immediate bearing on prognosis. It is, however, his impression that stones arise secondarily in chronic carriers.

7. Sex incidence.

Because the carrier state arose in circumstances of sex segregation no conclusions can be drawn from the series.

8. Mixed Carriers.

One of the nine was a mixed carrier of S. typhi and S. paratyphi B.

9. Urinary Overspill.

The observations of Browning et al. that bacilli occasionally occur in the urine of chronic carriers is confirmed.

10. Widal Tests.

The results of Widal Tests are variable and of little practical value, but the post-operative persistence of "O" agglutination in case No. 2 is unique in the series and this was the patient who relapsed.

11. The contention of Badia that patients over the age of 45 with a long history are poor surgical risks is not supported by the results in this series.

12. Danger to carriers from their latent infection.

That there is a danger to the carrier as well as to the community is shown by the fact that the patient M.S. developed an obstructive jaundice. Several of the carriers had stones and some had attacks of cholecystitis or cholangitis. There seems to the writer as much justification for advising cholecystectomy in chronic alimentary carriers as for advising the operation for chronic gall-bladder disease in the general population - possibly more.

13. Surgical v medical measures.

Efforts to cure the chronic enteric alimentary carrier state by medical measures have covered a wide field of therapy and with the discovery of modern chemotherapeutic and antibiotic agents, it seems to have been assumed that it would only be a matter of time before the carrier state could be eliminated by their use. Time, however, marches on and still there are foci of carriers from whom the general medical conscience is conveniently shielded. For them hope of cure is wearing thin and it is the belief of the writer that they should be promptly afforded the benefits of surgical treatment.

14. Biochemical aids.

The most useful of the various biochemical tests which have been employed in the pre- and post-operative investigation of this group of patients has undoubtedly been the serum bilirubin. It has been found to show a relatively higher reading in those carriers who have shown a high excretion frequency and to show a rising level in the case inwhich relapse occurred even before positive stool cultures became apparent.

15. Follow-up criteria.

Experience of the nine carriers in this work suggests that the minimum criterion for post-operative follow-up is the finding of negative stool cultures for 12-24 months preferably examined at fortnightly intervals. Monthly serum bilirubin levels should not show a significant rise.

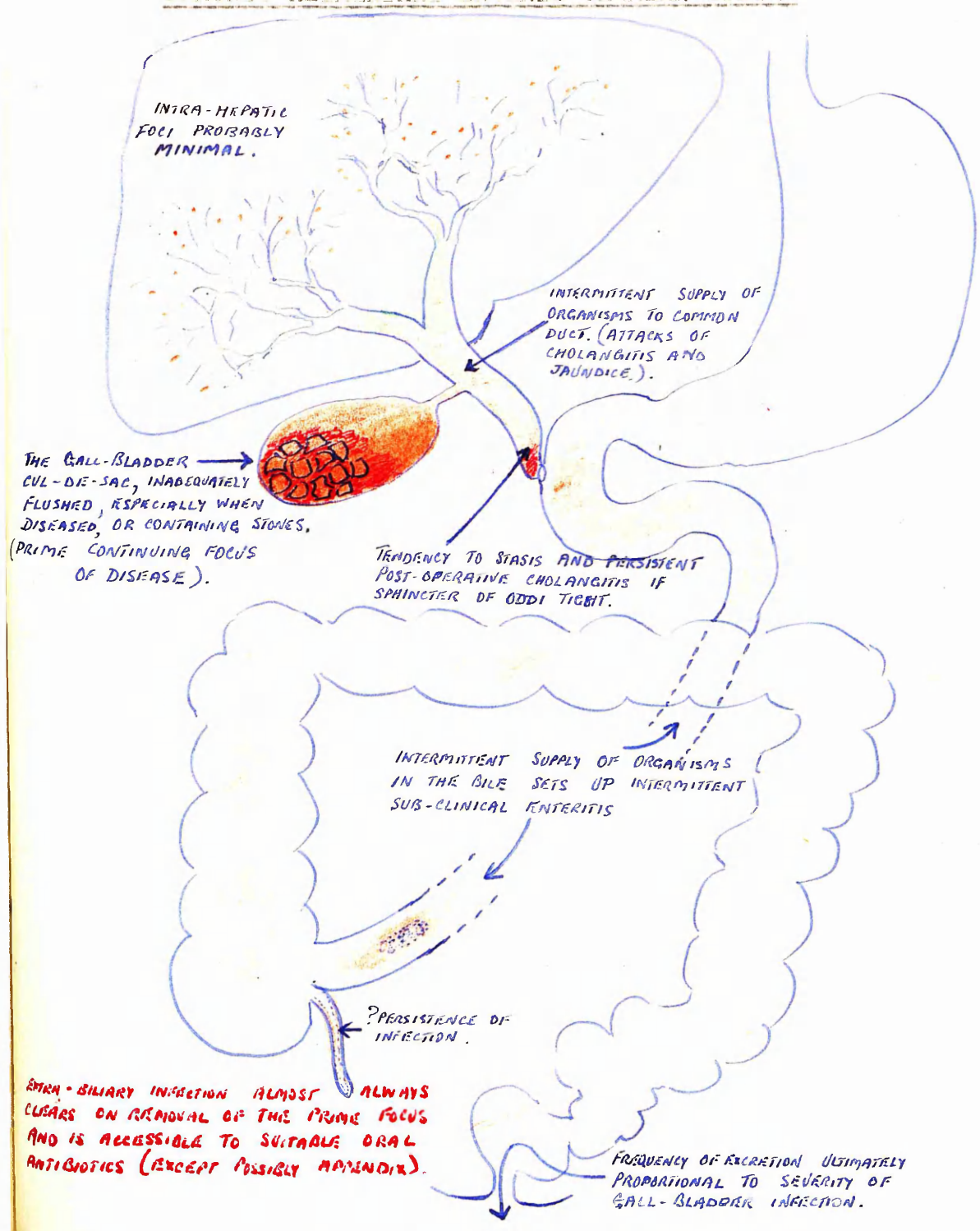
16. Antiseptic masking.

The possibility of maskingthe carrier state by the use of efficient intestinal antiseptics should be borne in mind.

17. Blood sedimentation rate.

In the absence of other causes such as anaemia a persistently high blood sedimentation rate in the post-operative phase raises the suspicion of continuance of the carrier state.

DIAGRAMMATIC REPRESENTATION OF AUTHOR'S CONCEPTION OF THE SITUATION AND SUPPLY OF ORGANISMS IN THE CHRONIC ALIMENTARY ENTERIC CARRIER STATE.



IRRESPECTIVE OF WHETHER THE CONCLUSIONS IN THIS WORK ARE FINALLY VINDICATED WITH THE PASSAGE OF TIME, IT IS THE FIRM BELIEF OF THE WRITER THAT, IN THE FORESEEABLE FUTURE, NO METHOD OF TREATMENT OF THE CHRONIC ALIMENTARY ENTERIC CARRIER WILL BE COMPLETELY EFFECTIVE UNLESS IT INCLUDES CHOLECYSTECTOMY.

THE ENTERIC PROBLEM IN SCOTTISH MENTAL INSTITUTIONS.

In view of the successful results in the Bellsdyke series of carriers, the writer decided to carry out a survey to determine the extent of the problem in Scottish Mental Institutions. Letters were written to the Superintendents of thirty-eight hospitals and institutions. A total of thirty-six replies were received and the following list indicates the numbers found in three situations.

Baldovan Institution, Dundee..... 18
Craig Dunain Hospital, Inverness..... 7
Hawkhead Hospital, Glasgow..... 12
Total.... 37 carriers.

It is suggested that the methods, facts and conclusions relating to the Bellsdyke series of cases should be placed before the R.M.P.A. and that consideration should be given to the possibility of treatment of the 37 carriers following the principles established by the present work.

THE PROBLEM ABROAD.

An indication of the extent of the carrier problem abroad is given by the following figures quoted in the literature:-

Year.	Place.	Estimated No. of enteric carriers.
1937	Baltimore	158
1947	Washington State.	38
1948	Washington State.	44
1957	Ireland	285

S E C T I O N 1X.

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S E C T I O N X.

Appendix A.

Appendix B.

Appendix C.

ADDENDUM

APPENDIX A.

FURTHER LINES OF RESEARCH INDICATED FROM THE PRESENT WORK.

It is not understood why certain antibiotics e.g. chloromycetin are apparently active against enteric organisms in vitro and of value in the treatment of acute enteric fever and yet have little or no effect on the carrier state. It would seem likely that antibiotics are carried to the gall-bladder wall in the blood stream although in chronic carriers with chronic inflammatory change in the wall the blood supply may be diminished.

If Garbat's view that the gall-bladder merely acts as a test-tube for the multiplication of the organisms, is accepted then it is important to know whether antibiotics are excreted in the bile in quantities sufficient to have a bactericidal or bacteriostatic effect. It should be possible to discover whether this is so by investigations carried out on a series of general hospital patients having cholecystectomy for chronic cholecystitis and lithiasis, not of enteric origin. Such patients could be given pre-operative courses of antibiotics and at operation, specimens of gall-bladder bile and common duct bile taken for assay.

Such an investigation is in hand.

The possibility was considered that the failure of antibiotics in the carrier state was due rather to the development of resistance in the organisms. The S. paratyphi B. recently isolated from case No. 2 was, however, found to be sensitive to all the common antibiotics.

APPENDIX B.

METHOD OF ISOLATION OF SALMONELLA GROUP OF ORGANISMS FROM FAECES.

Specimens were collected in screw-capped waxed cartons and were normally received in the laboratory during the forenoon. Immediately on receipt, Sodium Selenite 'F' enrichment medium was poured into the carton.

The carton was then incubated until the late afternoon when the stool was inoculated to McConkey's medium and Desoxycholate Citrate Agar.

The normal routine procedure of isolation of organisms of the Salmonella group was practised, i.e. plates were examined after 24 and 48 hours' incubation. Non-lactose-fermenting colonies were 'picked off' and examined for their fermentation properties.

Identification was completed by serological tests with the appropriate specific antisera.

APPENDIX C.

POST-OPERATIVE PHOTOGRAPHS OF THE NINE CARRIERS.

I am grateful to all those whose co-operation has enabled me to carry out this work, especially to Dr. A.P. Russell and the staff of Bellastyke Mental Hospital, to Dr. R. Rankin and the staff of the Pathology Dept., to Dr. D.R. Harper and the staff of the Radiology Dept. — and to the patients.

R.G. Shaw.
Mar., 1959.

D.S.

CASE N°5.

H. McD.

CASE N°8.

W. F.

CASE N° 9.

H. Mc M.

CASE N° 4.

J. C.

CASE N° 2

J. Cr.

CASE N° 6.

M. S.

CASE N° 1.

T. B.

CASE Nº 7.

J. K.

CASE N° 3.

THE NINE CARRIERS.

A D D E N D U M.

Bellsdyke Mental Hospital,

LARBERT.

September 1959.

Since the completion of this thesis in early March 1959 the progress of the nine carriers has been observed for a further period of six months. The patients have now been meticulously examined for more than a year following operation - in one case for a period of two and one half years. The results, summarised in the report which follows, lend further weight to the conclusions already drawn.

PROGRESS OF CASE No. 2 PATIENT J.C.

This is the patient whose relapse was forecast and who developed a positive stool culture in February 1959.

After his secondary operation, which was performed on 12th February 1959 convalescence was quite uneventful. The common bile-duct was drained by "T-tube" for a period of six weeks. No positive cultures were obtained and the opportunity was taken of administering the following antibiotics at intervals.

Streptomycin	1 gm. intramuscularly.
Chloromycetin	250 mgms. orally.
Chloromycetin	1 gm. orally.
Achromycin	250 mgms. orally.
Terramycin	250 mgms. orally.
Terramycin	200 mgms. intramuscularly.
Polymixin	500 mgms. intramuscularly.

No trace of any of the antibiotics could be found in the common duct bile.

When this investigation had been completed a twice-daily common duct lavage was instituted using a solution containing ½ gm. of neomycin and this was continued until the removal of the "T-tube" on 25th March, 1959. Before the

tube was removed, however, an injection of radio-opaque dye was made into it and the patient was screened. The dye was seen to flow freely into the duodenum through a patent orifice.

Since this time the carrier has remained clinically well without any trace of icterus and his investigations have been continued.

Stool Cultures.

Stool cultures have been made, as before, at fortnightly intervals. No further positive cultures have been obtained since the single positive in February i.e. the last thirteen consecutive cultures have been negative.

Liver Function Tests.

The serum bilirubin level dropped immediately following operation.

↓ SPHINCTEROTOMY & DRAINAGE.

NOV. '58	DEC. '58	JAN. '59	FEB. '59	MAR. '59	APR. '59	MAY. '59	JUN. '59	JUL. '59.
2·4	0·4	2·0	3·5	1·1	1·0	1·5	1·1	1·15

mgms/100ml.

The otherliver function tests remained normal.

Sedimentation Rate.

Average E.S.R. over a four-month pre-operative period 25/50mms.
Average E.S.R. over a four-month post-operative period 16/34mms.

Widal Reaction.

The S. para B. "O" titre disappeared from the serum immediately following the secondary operation.

↓ SPHINCTEROTOMY & DRAINAGE.

	NOV. '58	DEC. '58	JAN.	FEB. '59	MAR. '59	APR. '59	MAY '59	JUN '59	JUL. '59.
S. PARA B - "O"	-	1/50.	1/25.	1/25.	-	-	-	-	-
S. PARA B - "H"	-	1/250	1/250	1/500	1/250	1/500	1/250	1/250	1/500

A watch will of course still be kept on this patient's stool cultures but it is contended that the post-operative progress of this case gives further proof of the role of biliary stasis in perpetuating the carrier state. The indications are that this patient's infection has now very probably been eliminated.

DETECTION OF CHLOROMYCETIN IN GALL-BLADDER BILE.

In several patients having cholecystectomy for chronic cholecystitis and stones in Falkirk Royal Infirmary chloromycetin has been administered in dosages of 250 mgms. orally every six hours for two days before operation, 200 mgms. intra-muscularly two and one half hours before operation and 1 gm. intra-muscularly two and onehalf hours before operation. In no case has the antibiotic been detected in the gall-bladder bile after operation.

FOLLOW-UP OF THE MAIN BODY OF CARRIERS.

In the remaining eight carriers stool culture examinations have been made at fortnightly intervals. In no instance has any further positive culture been obtained, and there has been no indication from collateral studies of any likelihood of relapse.

PRESENT STATUS OF THE REMAINING 8 CARRIERS.

PATIENT	NO. OF CONSECUTIVE NEGATIVE STOOL CULTURES SINCE OPN	PERIOD OF POST-OP. OBSERVATION
M.S.	* 52	2 YEARS 6 MONTHS
T.B.	28	1 YEAR 2 MONTHS
J.Cy.	26	1 YEAR 2 MONTHS
D.S.	26	1 YEAR 1 MONTH
H.M°M.	26	1 YEAR 1 MONTH
H.M°D.	26	1 YEAR 1 MONTH
W.F.	26	1 YEAR 1 MONTH
J.K.	22	1 YEAR 1 MONTH.

The above results are infinitely better than those achieved by antibiotics in any series yet published.

* FORTNIGHTLY CULTURES

The dramatic cessation of excretion of enteric organisms by the nine alimentary carriers following cholecystectomy and neomycin therapy and the later course of the single carrier who relapsed together with the results of the academic investigations carried out, lead the writer inescapably to the following conclusions.

1. The gall-bladder and bile-duct system are the seat of the residual infection which is responsible for the faecal excretion of enteric organisms in the chronic alimentary carrier.

2. The removal of the gall-bladder cul-de-sac and the establishment of free biliary drainage are essential, in the present state of our knowledge, to the elimination of the carrier state. It is believed that neomycin played a subsidiary role and that it is capable in some carriers of killing the organisms in the intestine only.

3. It seems unlikely that in the foreseeable future antibiotics will cure the biliary enteric infection. (It is accepted that they will not cure chronic cholecystitis caused by other organisms). The writer believes that the use of antibiotics should be reserved for those cases which still may show residual infection after surgical treatment.