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INTRAVENOUS CHOLANGIO-CHOLECYSTOGRAPHY WITH "BILIGRAFIN"

ITS VALUE AS COMPARED WITH THE ORAL CONTRAST METHOD

BY

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[WITH SPECIAL PLATE]

Intravenous cholecystography was first introduced by Graham and Cole in 1924, but, owing to the relatively high degree of toxicity of the phenolphthalein compounds employed, its clinical use was almost completely abandoned when a number of effective and less toxic oral contrast media became available. The intravenous method of visualization of the biliary tract has recently received a fresh impetus with the introduction of the new contrast medium "biligradin" by Messrs. Schering, available in this country since 1954. As this dye appears to offer an advance in the accurate diagnosis of diseases of the biliary tract, the benefits which may be derived clinically from its use, and the subject generally, would seem worthy of review.

Pharmacology and Toxicity

"Biligradin intravenous" is the disodium salt of N:N'-adipic-di(3-amino-2:4:6-triiodobenzoic acid), in a watery solution, which is practically isotonic to normal saline. The substance is of very low toxicity. Winzer *et al.* (1954) found in experiments on rats that the lethal dose of biligradin is 3.4 g. per kg. body weight; this compares very favourably with the lethal dose of most oral contrast media for cholecystography, which is in the region of 0.4 g. per kg. body weight. It is therefore not surprising that the drug is very well tolerated.

This dye has been in wide use in various countries and there are reports on large series of cases—for example, by Frommhold (1953), Hornykiewytch and Stender (1953, 1954), and Gaebel and Teschendorf (1953, 1954) from Germany; Caroli *et al.* (1954) from France; Huber and Stoessel (1954) from Switzerland; Glenn *et al.* (1954) and Orloff *et al.* (1954) from the United States, where the dye is marketed under the name of "cholografin"; Sethna (1954) from India; Sutton and Tillett (1954) and Aldridge (1955) from Great Britain. Only mild side-reactions were recorded by these authors. In our own series of 106 cases we have not seen any severe reactions, but there have occasionally been slight nausea, a feeling of heat or of flushing in the face, and one of our patients had a mild and transient erythematous rash. Though biligradin is an eminently stable compound and does not liberate iodine in the body, it is generally agreed that it should not be used in cases of known iodine idiosyncrasy. However, the slight allergic reactions which occasionally occur are thought to be due to sensitivity to the whole molecule rather than to free iodine.

Generally our impression is that biligradin is better tolerated than the dyes used for oral cholecystography. The frequent side-reactions of oral cholecystography, such as nausea or vomiting, are rare, and diarrhoea is unknown after biligradin.

Technique of Examination

We have used 40 ml. of biligradin as a routine, as this amount did not seem to produce any more side-effects than 20 ml. and gave pictures of better diagnostic quality. Examination has recently been simplified by the introduction of "biligradin forte." This is the methylglukamine salt of the compound in a more concentrated solution, 20 ml. of which is adequate for diagnostic purposes. The injection can be completed in three minutes. Side-reactions are also negligible. Intravenous examination can easily be fitted into the routine of the x-ray department. For the bile ducts films are taken 30 and 50 minutes, and for the gall-bladder up to 3 hours, after the injection. Upright spot films under screen control are taken if necessary. Between exposures the patient is allowed to move about freely. Small accidental paravenous injections cause a slight local burning sensation, but no necrosis or other after-effects.

It has been suggested that oral cholecystography and the intravenous examination can be carried out in one session. We had not originally the courage to do this, in view of the possible cumulative toxic effects of the two dyes, and preferred to leave an interval of at least two days between the two examinations, but recently, in order to come to a quick conclusion, we have examined several patients in this way without noticing any unfavourable effects. We have not used any of the drugs recommended to provoke spasm of the sphincter of Oddi, such as neostigmine, morphine, pethidine, or paregoric, the results usually being adequate without such complicating procedures.

When cholangiography only is to be performed the patient is kept fasting, but when visualization of the gall-bladder also is required a fatty meal is given 1½ hours before the injection, in order to empty the gall-bladder as completely as possible. In agreement with Aldridge we have the impression that this accelerates filling of the gall-bladder with dye and facilitates uniform mixing of dye and bile.

Concentration in the Bile

Soon after injection biligradin appears in a high concentration in the bile, the flow of which is increased by the strong choleretic effect of the drug. Frommhold (1953) quotes from animal experiments and observations of patients with external biliary fistulae that the concentration of

biligradin in the bile reaches 30 to 100 times that in the blood within 10 to 15 minutes of the injection. By this time the hepatic and common bile ducts are already clearly outlined. The filling of the gall-bladder follows later by gradual infiltration of the dye by way of the cystic duct towards the fundus. Full filling of the gall-bladder takes from one to three hours. Visualization of the biliary system by biligradin thus operates in the reverse order to that which occurs in oral cholecystography. In oral cholecystography the original concentration of the dye is not enough to visualize the ducts or gall-bladder, and further concentration in the gall-bladder is required to render that organ opaque.

Shehadi (1954) has shown that in a high percentage of cases the common bile duct can also be demonstrated by oral cholecystography while the gall-bladder is emptying after a fatty meal. Twiss *et al.* (1954) have even demonstrated that it is possible to visualize the common duct by oral cholangiography in cholecystectomized patients. Their rather elaborate techniques appear, however, to be unnecessary in view of the more reliable results obtainable by the new intravenous method. With biligradin visualization of the common duct occurs with great regularity, the duct becoming visible whether the gall-bladder has filled with the dye or not, and in patients whose gall-bladders have been removed. As the filling of the gall-bladder with biligradin is a passive process dependent only on the cystic duct being patent and its lumen adequate, and as it does not require the concentrating power of the gall-bladder wall, it is sometimes possible with biligradin to visualize a gall-bladder which has failed to show with oral cholecystography. A fact to be remembered is that on occasions the thick bile in the gall-bladder mixes poorly with the dye. This leads to unequal densities, and may simulate a filling defect due to calculi, but the phenomenon disappears when time is allowed for adequate infiltration and mixing to take place.

It must be emphasized that in oral cholecystography the concentration of the dye or its failure to concentrate in the gall-bladder remains a valuable test of the function of that organ. A negative oral cholecystogram may be the only radiological sign of inflammatory or metabolic disease of the gall-bladder in cases where the findings with biligradin are normal. We therefore believe that for the time being these two methods are complementary and that neither can fully replace the other. The same point was stressed by Graham in a recent discussion on a paper by Glenn *et al.* (1954).

Jaundice

In obstructive jaundice results with biligradin are consistently poor, it being rarely possible to outline either bile ducts or gall-bladder, though the injection of the dye does not cause any harm. Such failure is probably due to the presence of inspissated bile in the tract, preventing the dye from infiltrating adequately. Useful results have, however, been obtained as soon as the jaundice begins to subside. We have demonstrated stones in the common duct in three of our patients under such circumstances (Special Plate, Figs. 1, 5, and 7). On the other hand, a case of haemolytic jaundice which was examined with biligradin produced a perfect filling. This patient had a splenectomy, during which stones were felt in the gall-bladder, which was left intact. As the jaundice showed little sign of improvement after the operation the question of an obstructive factor arose. Biligradin filled the stone-containing gall-bladder and demonstrated a slender common duct without stones, thus clearly eliminating an obstructive element.

Excretion of Biligradin

With normal liver function 90% of biligradin is excreted by the liver, about 10% by the kidneys. No reabsorption of the dye takes place in the bowels and its bulk is evacuated with the stools. Trebbin (1954) found that liver damage may lead to a rise in urinary excretion of up to 50% of the intake of the dye and to a protraction of its excretion time to several days. While traces of a transient intravenous pyelogram are not uncommonly present when liver function

is adequate (Special Plate, Fig. 4), in cases of liver insufficiency a prolonged pyelogram may be seen with greater regularity. The kidney takes over when the liver fails. Simple loss of portions of liver substance does not seem to affect the excretion of biligradin to a detectable extent. In three of our cases with extensive neoplastic infiltration of the liver, but without clinical jaundice, good excretion of the dye occurred.

Plan of Investigation

Altogether we examined 106 patients with biligradin—75 with an intact gall-bladder and 31 after cholecystectomy. The first group consisted of strictly selected cases, in all of which oral cholecystography was performed in the first instance. The examination with biligradin was undertaken only when oral cholecystography had failed to produce a satisfactory shadow of the gall-bladder or when it was considered that the questions raised by the clinical aspect of the case had not been adequately answered. It was thus attempted to assess the comparative values of oral cholecystography and intravenous cholangio-cholecystography. It may be mentioned that for oral cholecystography the double-dose method was employed, and that a series of upright spot films under screen control was taken in all cases with a clearly visible gall-bladder. A conclusive result regarding the condition of the gall-bladder itself can usually be obtained with this method alone, and in only a minority of cases did we find it desirable to continue the examination with biligradin.

Patients with Intact Gall-bladder

The results in the 75 cases with intact gall-bladders in which both tests were performed are given in Table I.

TABLE I.—Results of Intravenous Cholangio-cholecystography in Patients with Intact Gall-bladders

A. After Unsuccessful Results of Oral Cholecystography			
1. Ducts and gall-bladder filled:			
a. With stones—			
i. In the gall-bladder alone ..	16		
ii. In the common duct alone ..	1		
iii. In the gall-bladder and common duct	3		
		20	
b. Without stones	6		
c. Unclassified	1		
		27	
2. Hepatic and common ducts only filled ..	28		
3. No demonstration of gall-bladder or ducts ..	3		
		58	
B. After Successful Oral Cholecystography:			
1. Stones in common duct	1		
2. Normal bile ducts	15		
3. No demonstration of gall-bladder or ducts ..	1		
		17	
Total		75	

A. Biligradin Examination After Unsuccessful Oral Cholecystography

In the 58 cases in this group the gall-bladder had either not filled with the oral method or had given such a faint shadow that no definite diagnosis as regards calculi could be made. Among these 58 cases the gall-bladder filled with biligradin in 27, thus indicating the patency of the cystic duct. Stones were shown in 20 of these cases—in 16 in the gall-bladder alone, in one in the common duct alone (Plate, Fig. 1), and in three in both gall-bladder and common duct. In all but one case the presence of stones had remained doubtful after oral cholecystography. The exception had a solitary giant stone in the gall-bladder, whose small opaque centre had been seen as a faint shadow in a plain film but whose actual size and position were demonstrated only by biligradin.

The case with the solitary stone in the common duct (Plate, Fig. 1) deserves special description. This patient had just recovered from an attack of obstructive jaundice. An oral cholecystogram showed a very faintly filled gall-bladder of normal size. With biligradin a large stone was demonstrated high up in the common duct approximately at its junction with the cystic duct, and only an incomplete filling of the gall-bladder was obtained. At operation to remove the stone the wide cystic duct and the gall-bladder

were found clear of stones. It appears that the stone in the common duct had intermittently occluded the cystic duct.

Two of the three patients with stones in the gall-bladder and common duct had never been jaundiced. Oral cholecystography had failed to outline the gall-bladder and had not shown any stones. The most spectacular of three cases showing gross lobulations of the gall-bladder as well as calculi is illustrated in Fig. 2 on the Special Plate. At operation the deformities were found to be due to the gall-bladder being partly embedded in the substance of the liver. An interesting feature in each of these cases was that stones were found in the distal compartment only of the gall-bladder, where stasis must have been most marked. None of this pathological picture was visible on oral cholecystography.

One of the six cases with a normal intravenous cholangio-cholecystogram following the failure of oral cholecystography turned out to have a benign pyloric stenosis. Oral cholecystography is naturally condemned to failure by any abnormality preventing the absorption of the contrast medium, and the risk of a mistaken diagnosis of biliary-tract disease in such cases is well known. With the intravenous method mistakes of this kind can now be avoided. No such cause for unsuccessful oral cholecystography was, however, found in the other five cases without calculi (Table I, A1b), and in our view these illustrate the persisting importance of oral cholecystography, demonstrating the failure of a pathological gall-bladder to concentrate the dye.

The unclassified case (Table I, A1c) showed features of particular interest. It was one in which two large gall-stones causing intestinal obstruction had been removed from the jejunum a short time previously. The common and cystic ducts showed normal outlines with biligradin, but the gall-bladder was only faintly demonstrated with its fundus pulled strongly across towards the duodenum, in which much dye could be seen. The very faint gall-bladder shadow and its distorted position suggested a cholecysto-duodenal fistula with leakage of the dye into the duodenum. There were no obvious residual calculi in the gall-bladder.

In the 28 cases where the hepatic and common ducts only were outlined (Table I, A2), obstruction of the cystic duct was presumed. This was confirmed in all cases at operation, and found to be due to calculus. We have not so far encountered any case of neoplastic obstruction of the cystic duct, but would expect the appearances to be similar. In two patients a non-opaque stone in the cystic duct became outlined by biligradin during the examination (Plate, Fig. 3). Another patient had had more prolonged jaundice than would normally be expected with temporary impaction of a stone at the lower end of the cystic duct. Biligradin showed pronounced dilatation of the hepatic ducts and of the common duct above the junction with the cystic duct, but the lower end of the common duct also appeared dilated to some extent (Plate, Fig. 4), suggesting that a calculus, after being impacted for a time in the first position, had been held up at the ampulla before being passed into the duodenum. At operation fine grit and inspissated bile only were found in the cystic duct, and the common duct was clear, so that this may well have been the case. In cases presenting the clinical picture of "acute cholecystitis" biligradin usually shows a blocked cystic duct, even if the examination is delayed until the acute stage has subsided.

Of the last three cases, in which neither ducts nor gall-bladder were demonstrable by biligradin (Table I, A3), one had advanced hepatic cirrhosis and one was a case of recent obstructive jaundice. The third had recently undergone transduodenal excision of a small tumour at the ampulla of Vater: this apparently resulted in incompetence of the sphincter of Oddi, with consequent entry of air into the biliary tract and rapid leakage of dye into the duodenum. Another similar post-operative case, included in Group A2 in Table I, showed alternate filling of the common duct with dye and air in a series of films after biligradin injection. In such cases only the presence of dye in the duodenum may indicate that it has been excreted by the liver.

B. Biligradin Examination After Successful Oral Cholecystography

The discovery of stones in the gall-bladder with oral cholecystography does not necessarily reveal the full pathological picture, particularly in view of the possibility of calculi in the common duct. The incidence of calculi occurring in the gall-bladder alone was stated by Walters and Snell (1940) to be 87%, in the gall-bladder and common duct 7%, and in the common duct alone 6%; but Bernhard (1935) found the incidence of common-duct stones as high as 20% of all cases of calculus. The occasional absence of obstructive jaundice with common-duct stones has been emphasized by various authors. Four such cases were seen in our series, two pre-operatively and two after cholecystectomy. As these common-duct stones can be readily demonstrated with biligradin, intravenous cholangiography should be performed in every case before cholecystectomy is undertaken. This will usually indicate whether the common duct needs to be explored or not.

Group B of Table I comprises 17 cases where oral cholecystography had been successful but where clearer anatomical detail of the gall-bladder was desirable or there was a suspicion of stones in the ducts. One patient in this group was found to have stones in the common duct in addition to those already diagnosed in the gall-bladder (Table I, B1). This patient had just recovered from a first attack of mild transient obstructive jaundice. It was the unusual degree of clinical shock during an attack of biliary colic on admission to hospital that prompted the biligradin investigation (Plate, Fig. 5). Another case examined early in our series (Table I, B3) showed no shadow of biligradin in gall-bladder or ducts, though a functioning gall-bladder full of stones had been demonstrated by oral cholecystography. The reason apparently was that the biligradin examination had been carried out too soon after an attack of obstructive jaundice, probably due to temporary impaction of a stone, which had intervened since the cholecystography. Had this negative result occurred later in the series the intravenous examination would have been repeated. No stone was, however, found in the common duct at operation.

The remaining 15 patients in this group had normal common bile ducts. Among them were a few with a normal oral cholecystogram without stones, examined because of recent attacks of jaundice believed to be possibly obstructive. In none of these did we encounter stones in the common duct, and the jaundice had probably been due to infective hepatitis. It appears that the presence of common-duct stones affects the quality of the oral cholecystogram, and that good concentration of the dye in a gall-bladder free of stones makes it unlikely that stones are present elsewhere in the biliary system. A normal oral cholecystogram thus seems to remain a reliable sign of a healthy biliary tract.

Intramural Diverticulosis of the Gall-bladder

In one case among the 15 referred to above the examination was carried out because oral cholecystography had demonstrated a bilocular deformity of the gall-bladder. The patient was a young man with several years' history of biliary dyspepsia. The intravenous examination with biligradin showed delicate protrusions of dye outside the main lumen

Operative specimen of gall-bladder shown in Fig. 6 of Special Plate.

of the gall-bladder, best seen at the waist between the two compartments (Plate, Fig. 6). A diagnosis of intramural diverticulosis of the gall-bladder (cholecystitis glandularis proliferans; Aschoff-Rokitansky sinuses) was made, and this was confirmed at operation. The operative specimen (see photograph) demonstrates the gross leathery thickening of the wall of the lower compartment and shows cuts through some of the sinuses. According to the histological report (Dr. E. N. Trounson) there were also extensive inflammatory changes. This condition is now generally considered as associated with chronic inflammation of the gall-bladder (March, 1948; Bean and Culver, 1950; Lawler, 1952; Sutton, 1955). The radiological demonstration of such sinuses thus appears to justify the diagnosis of chronic cholecystitis. It is likely that many cases of this kind have escaped detection by oral cholecystography, for, in spite of the frequency with which these sinuses are seen in pathological specimens, their radiological diagnosis has been rare. This may in future be altered owing to the increased anatomical detail which biligradin can reveal even in a poorly functioning diseased gall-bladder.

Post-cholecystectomy Examinations

The second main group are patients who had undergone cholecystectomy. The results are given in Table II.

TABLE II.—Results of Intravenous Cholangiography in Post-cholecystectomy Patients

1. Without symptoms	..	..	..	..	..	11
2. With symptoms:						
a. Stones in common bile duct	..	..	..	..	..	5
b. Fibrosis of common bile duct	..	..	..	..	..	1
c. Demonstrable stump of cystic duct	..	..	..	..	..	4
d. Normal ducts	..	..	..	..	..	10
						20
Total	..	..	..	..	..	31

Normal Findings After Cholecystectomy

In the early stages of our investigation we examined 11 patients after cholecystectomy, without symptoms, in order to gain experience with regard to the range of normal findings. This subject has since been dealt with in greater detail by Don (1955). Visualization of the common duct was obtained in all cases. In most instances the duct was slender, measuring about 3 mm. in diameter, but in a few cases the duct measured up to 10 mm. It was noted that the time during which the common duct remained visible varied greatly; in some cases it was demonstrated up to several hours after injection. It seemed unlikely that these variations in the size of the duct or in the degree of spasm of the sphincter of Oddi, as indicated by the retention of dye, had any clinical significance. A grossly dilated common duct may be due to pre-operative obstruction which has been relieved.

Post-cholecystectomy Syndrome

Having excluded coincident peptic ulcer, hiatus hernia, chronic appendicular dyspepsia, and other possible causes of discomfort, there still remain a certain small number of patients in whom symptoms of a biliary-tract type continue or recur after cholecystectomy.

Stones in the Common Duct After Cholecystectomy

Moynihan, in his book *Abdominal Operations* (1926), claimed that the tiniest fragment of stone within the common duct could be detected by expert fingers. Most surgeons like to feel that this is the case, and in performing cholecystectomy do not open the common duct unless there has been jaundice or unless palpation raises the suspicion of stone or other obstruction. The fact remains, however, that occasionally a stone is missed during palpation of the common duct or has been lurking out of reach in one of the hepatic ducts and is allowed to remain, with consequent persistence of symptoms. It has been optimistically hoped in the past that these post-operative symptoms might be due to spasm of the sphincter of Oddi, but it now appears open to doubt whether such spasm in itself ever gives rise to symptoms.

Davidson *et al.* (1949) stated that in a series of patients with common-duct stone no less than 30% required operation because stones had been overlooked at previous cholecystectomy, and it is more disturbing still that Hughes *et al.* in 1948 and Thiessen in 1951 reported the discovery, at post-operative cholangiography, of retained stones in the common duct after choledochostomy in 24% and 15% of cases respectively. It is of interest also that Corff *et al.* in 1952 found that 41% of their patients with stones in the common duct had never been jaundiced. It is therefore of the greatest importance that intravenous cholangiography should be carried out as soon as possible when biliary symptoms recur after cholecystectomy, whether there has been jaundice or not. As recurring jaundice has always been an indication for laparotomy, the examination appears particularly important in the non-jaundiced patient. In the past, as there has been no non-surgical method of examining the common duct, there has been much speculation upon the cause of symptoms in these patients, with consequent delay and suffering. The advent of biligradin, however, provides a reliable method of demonstrating the common and hepatic ducts without laparotomy.

Among 20 patients examined because of symptoms following cholecystectomy, five had stones in the common duct. The cholecystectomy had been performed at varying times up to ten years previously. In four of the five the stones were clearly demonstrated by biligradin (Plate, Figs. 7 and 8) and corresponding numbers were removed subsequently at operation. Two of these (Plate, Fig. 8) had never been jaundiced. In one who had had recurring jaundice a rather wide and winding common duct was seen. At operation a small stone was found in the common duct which had not been diagnosed pre-operatively, but was seen on post-operative scrutiny of the films. It is to be hoped that with growing experience mistakes of this kind may be avoided.

A case with recurring jaundice after cholecystectomy and removal of stones from the common bile duct showed a rather complicated network of dilated branches of the hepatic ducts but no clear visualization of the common duct. The density of the hepatic-duct shadows was poor. This case proved at operation to have an extensively fibrosed common duct and early biliary cirrhosis (Table II, 2b). Although this is a solitary experience, we have the feeling that the picture may be characteristic of common-duct fibrosis with obstruction.

Small cystic-duct stumps were shown in four cases (Table II, 2c), but, although this condition has been held possibly responsible for symptoms in the past, the discomforts described by our patients passed off spontaneously.

Conclusions and Summary

Intravenous cholangio-cholecystography with biligradin is a quick, safe, and reliable method of examination in biliary-tract disease. Unfortunately it is usually ineffective in the presence of obstructive jaundice or severe liver insufficiency, although its attempted use in such cases is not harmful. It may be used as a supplementary method to oral cholecystography: (1) in cases in which oral cholecystography has been successful; to show clearer and more comprehensive anatomical detail and to demonstrate the possible presence of stones in the hepatic and common bile ducts; and (2) in cases where oral cholecystography has been unsuccessful; to differentiate between calculous and non-calculous disease of the gall-bladder and to determine the detailed location of stones within the tract.

A series of cases in both the above groups is described and illustrated. In most of the cases which were subjected to both types of examination it was found that the intravenous examination provided greater diagnostic information than oral cholecystography. Moreover, the intravenous method makes cholecystography independent of absorption of the dye in the alimentary tract.

For these reasons intravenous cholangio-cholecystography might be substituted for oral cholecystography as the primary method of investigation. From a surgical point of view this can usually be expected to give all the information required. Where, however, it is desired to assess the concentrating power of the gall-bladder it can be supplemented by oral cholecystography. In abdominal emergencies the use of biligrafin intravenously may offer a means of quick differential diagnosis by confirming or excluding the biliary tract as the cause of symptoms.

The fact that the common bile duct becomes outlined with great regularity represents the main advantage of the intravenous method. After cholecystectomy the injection of biligrafin offers the only practical non-operative method of examining the bile ducts.

We are indebted to our colleagues for allowing us to use some of their case notes. We are also grateful to our radiographic staff for the help they have given us, and to Miss A. J. Wright particularly for the prints.

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FUNGUS DISEASES OF BRITAIN*

BY

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During the past five years a number of different fashions in British medicine and biology have shown increasing interest in fungous diseases. Fortunately, at this time, too, observations made in various parts of the world have become more reliably comparable now that the old confusion in nomenclature has disappeared. The most widely accepted present-day opinions in this subject have been summarized elsewhere (Riddell, 1951a, 1951b, 1952), but it is perhaps timely that recent trends in the study of these diseases in Britain should be reviewed.

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Dermatophyte Infections

The recrudescence of epidemic ringworm of the scalp which occurred largely as a result of relaxation of preventive measures during the second world war has now abated, and *Microsporum* infections of the scalp now involve small groups of children only sporadically. Dr. H. G. Adamson, who died only last year, was responsible for the first fundamental observations upon the pathogenesis of this disease 60 years ago in Britain, but, surprisingly enough, the work was not adequately followed up until Kligman's studies on experimental infections, published in 1955 from Philadelphia.

TABLE I.—Susceptibilities of Different Keratin Structures to Infection by Dermatophyte Species

	Skin	Nail	Hair (Scalp)
Microsporum:			
<i>M. audouini</i>	+	—	++ (SSE)*
<i>M. canis</i>	++	—	++ (SSE)*
<i>M. gypseum</i>	++	—	± (SSE)
Trichophyton:			
<i>T. mentagrophytes</i>	++	—	± (SSE)
<i>T. discoides</i>	++	—	± (LSE)
<i>T. interdigitale</i>	++	—	—
<i>T. rubrum</i>	++	++	—
<i>T. sulphureum</i>	++	+	++ (E)
<i>T. violaceum</i>	+	+	++ (E)
<i>T. schoenleini</i>	+	+	++ (E)†
Epidermophyton:			
<i>E. floccosum</i>	++	±	—

(SSE)=Small-spored ectothrix hair infection. (LSE)=Large-spored ectothrix hair infection. (E)=Endothrix hair infection. * Bright yellow-green fluorescence produced in hair. † Dull green fluorescence produced in hair.

It is now possible to attribute the characteristic wide sheath of small spores indiscriminately arranged around a *Microsporum*-infected hair shaft to sporulation of much-branching fungous hyphae as they re-emerge into a follicle from the hair cortex. The sheath of spores is not derived from fungous hyphae growing down into a follicle and entwining the hair, as was previously supposed, and as is assumed to be the case in ectothrix infections caused by those *Trichophyton* fungi which infect lower animals as well as man. It would be difficult to repeat Kligman's experiments with *Trichophyton* species which produce only human infections, for these are of low pathogenicity. As to why fungous elements should completely disappear from the hair surface in this last type of infection and leave only an endothrix disposition of fungous hyphae and spores is an intriguing but unsolved problem.

An explanation for the differences which *Microsporum* and *Trichophyton* fungi exhibit in the production of fluorescing substances while growing as parasites in the hair-root keratin has been sought by Chattaway and Barlow (1954), using paper chromatography and electrophoresis. The production of three fluorescent fractions was demonstrated in *Microsporum* infections, and two additional fractions in infections due to the favus *Trichophyton*. Whether similar chemical substances are produced in hair by other *Trichophyton* species in quantities undetectable by ultraviolet light has not been investigated, nor whether they are produced in other keratin structures. Ringworm fungi virtually behave as saprophytes, for they invade only mature keratin and do not parasitize parakeratotic cells. An explanation for the rather specific way in which they attack different kinds of keratin has yet to be found (Table I). Some fungi have a predilection for certain body regions, and there are forms of tinea infection which differ greatly in their sex incidence. Chemical and/or physical differences in keratin structure, possibly occurring at different cutaneous sites, may in part determine this issue, and it has been suggested that the completeness of naturally occurring cross-linkages between radicals of the keratin molecule may be important in this respect.

Barlow and Chattaway (1955) have shown that measures which encourage the breakdown of disulphide linkages and hydrogen bonds of hair keratin facilitate fungal attack in

R. W. W. HARDIE AND M. ISRAELSKI: INTRAVENOUS CHOLANGIO-CHOLECYSTOGRAPHY

FIG. 1.—Large solitary stone in upper part of dilated common duct, opposite junction with cystic duct, causing partial block of cystic duct and incomplete filling of gall-bladder (arrowed). At operation no stones found in gall-bladder or cystic duct. Biligrafin examination soon after attack of obstructive jaundice. Large calcified primary focus in base of right lung.

FIG. 2.—Gross deformity owing to tunnelling of portions of gall-bladder through liver tissue. Portions bulging out of liver simulate diverticula. Stones in distal compartment. No filling at oral cholecystography.

FIG. 3.—Cystic duct blocked by non-opaque stone (arrowed) becoming outlined with biligrafin (one hour after injection).

FIG. 4.—Dilated hepatic and common ducts. Dilatation most marked above junction of cystic with common duct. Suggests recent impaction of calculus at junction, with further hold-up at ampulla before passage into duodenum. Cystic duct still obstructed. Also an accidental pyelogram (arrowed). No filling at oral cholecystography.

FIG. 5.—Multiple stones in gall-bladder and three stones in common duct (one hour after injection). Following recent attack of colic and obstructive jaundice.

FIG. 6.—Intramural diverticulosis of gall-bladder (one hour after injection).

FIG. 7.—Stone at lower end of dilated common duct, after cholecystectomy. (30 minutes after injection.)

FIG. 8.—Two large stones in dilated common duct after cholecystectomy. No history of jaundice. (30 minutes after injection.)