

DUODENAL CATHETERIZATION

(EMPLOYING PITUITRIN AND OLIVE OIL)

IN THE DIAGNOSIS OF GALL-BLADDER DISEASE.

BY

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any patient requiring investigation of the gall-bladder, one will not lose sight of the two biliary decubiti - as these in the early stages of biliary disease - is essentially a test of the contractile capabilities of the gall-bladder.

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During a visit to Berlin where some time was spent with Kalk, one was very much impressed by his enthusiasm for biliary drainage, and, in particular, for the use of pituitary extracts in this test, as an aid to diagnosis in gall-bladder disease. In view of the facts that the whole subject of biliary drainage is comparatively new, that Kalk was so enthusiastic regarding his own method, and that, in this country, comparatively little has been done in this connection, it was decided to endeavour to verify or disprove Kalk's opinions regarding the value of this test using pituitrin (combined in some cases with olive oil). As Kalk's method is somewhat complicated and not practicable in hospitals in this country, where the house-staffs are not so large and where not so much time can be devoted to the method as used by him, his procedure was simplified with a view to rendering it, if found of value, capable of routine application in any patient requiring investigation of the function of the gall-bladder: one must not lose sight of the fact that biliary drainage - as done in the series of cases investigated here - is essentially a test of the function-capabilities of the gall-bladder.

ORIGIN OF DARK BILE OBTAINED IN BILIARY DRAINAGE.

The possibility of obtaining bile from the gall-bladder was first raised by Meltzer<sup>1</sup> who suggested that the introduction of magnesium sulphate into the duodenum would lead to relaxation of the sphincter of Oddi and the passage of bile from the gall-bladder. One does not intend to discuss here the points for and against Meltzer's theory as regards contrary innervation, a subject which has been widely discussed since the reports of his work first appeared. Lyon<sup>2</sup> followed Meltzer's suggestion, using magnesium sulphate, and he was the first to attempt to utilise biliary drainage as a diagnostic and therapeutic measure in cases of gall-bladder disease. Kalk<sup>3</sup> mentions that Stepp shortly afterwards commenced to use Wittepeptone, another substance regarded as capable of producing an outflow of bile from the gall-bladder: both magnesium sulphate and Wittepeptone were introduced into the duodenum after a tube had been passed into that part of the small intestine. Subsequently Stepp employed, in a similar manner, oil after its cholekinetic action had been proved by Klee and Klüppel. After the introduction of these substances into the duodenum, a flow of dark bile was observed by Lyon and Stepp, and they concluded that this bile represented the contents of the gall-bladder, and that its appearance was directly attributable to the use of magnesium sulphate, oil and peptone.

The contention of Lyon and Stepp that the dark bile thus obtained was bile from the gall-bladder was opposed strongly by - amongst others - Crohn, Reiss and Radin<sup>4</sup> and Bassler, Luckett and Lutz<sup>5</sup>. Those investigators, who opposed the views of Lyon and Stepp as regards the origin of the dark bile obtained after the use of

magnesium sulphate, etc., and did not base their objections on results obtained from animal-experiments, produced, in support of their opposition, certain arguments. Firstly - one can, by the repeated use of magnesium sulphate, bring about successive appearances of dark bile, an occurrence which is definitely - they hold - against the view that this dark bile represents the contents of the gall-bladder: if this bile were from the gall-bladder it should not be possible to produce repetitions of the flow: secondly - the transition from light to dark bile is gradual, which is explicable only by assuming the dark bile comes from liver: thirdly - it is possible after cholecystectomy to obtain dark bile by the use of magnesium sulphate and Wittepeptone: the origin of the dark bile obtained after the use of these substances must therefore be the liver, which has concentrated the bile.

These arguments may be answered as follows:-

1). cholecystographic observations have shewn that a complete emptying of the gall-bladder is not always seen after the use of certain cholekinetic substances e.g. magnesium sulphate, peptone, pituitary extracts. As a rule the emptying appears to be only partial since the gall-bladder shadow does not disappear completely: it is therefore obvious that, if the gall-bladder has been only partially emptied, it might be possible to bring about again an outflow of bile from the viscus. Kalk<sup>3</sup> holds however that when substances such as pituitrin and oil are used, the occurrence of a second response on the part of the gall-bladder is unusual because these two substances are capable of causing strong contractions of <sup>the</sup> gall-bladder and more or less complete emptying. It will be seen later that it was possible in this series of cases to observe, on occasion, a second appearance of dark bile.

2). Kalk<sup>3</sup> refers to Einhorn who supported the view that the dark bile obtained after the use of cholekinetic substances comes from the liver, because the transition from light to dark duodenal contents is gradual. Einhorn's opinion does not receive support from the cases investigated here in which the transition was comparatively sudden. Kalk<sup>3</sup> has also observed that the change in colour of the bile was sudden and certainly not gradual. One must remember that magnesium sulphate and Wittepeptone possess choleric as well as cholekinetic properties, as has been shewn by Brugsch and Horsters<sup>6</sup>: these two substances therefore do produce a flow of bile from the liver in addition to the flow from the gall-bladder: and one must also remember that in cases of "catarrhal jaundice" (as the jaundice goes) and of pernicious anaemia, the bile secreted by the liver is of a higher concentration than is usually seen (the writer has seen such cases). These cases are however exceptional, and pituitary extracts and oil possess no choleric but only cholekinetic properties, as was shewn by Erbsen and Damm (quoted by Kalk<sup>3</sup>), and can cause flow<sup>a</sup> of dark bile. It may therefore be presumed that the gall-bladder is the seat of the dark bile observed during duodenal catheterization after the use of certain substances: if it came from the liver the transition would be certainly gradual.

3). One must admit that after cholecystectomy it is possible to obtain dark bile when one remembers the work of Judd<sup>7</sup> and Judd and Schmieden (referred to by Held and Goldbloom<sup>8</sup>): they showed that after cholecystectomy the small intra-hepatic ducts dilate considerably for the purpose of concentrating bile and thus compensate for the loss of the gall-bladder. Stepp and Düttmann<sup>9</sup> have remarked on this occurrence too, but hold that the dark bile obtained in such

cases is never so dark as is the bile, allegedly from the gall-bladder in normal cases. This has been confirmed by Kalk<sup>3</sup> and Dicks<sup>10</sup>, the latter of whom noted the absence of the usual sequence of flow, although he did find the bile to be somewhat darker than in normal cases. One may take it therefore that after cholecystectomy dark bile may be obtained, but it is quite different as regards amount of pigment-content from gall-bladder bile, and its presence is to be explained by compensation on the part of the duct system for the loss of the gall-bladder.

Certain workers that have used animals in experiments or have made observations on the human being during operation deny the possibility of obtaining dark bile after the use of such substances as magnesium sulphate, peptone, oil, pituitrin. The results obtained in animal-experiments must obviously be accepted with reserve i.e. where operative measures have been undertaken. Some of the gall-bladder experiments on animals were done in a very detailed manner and with much manipulation and, in view of the delicate mechanism of the gall-bladder, it is easily understood how, even by opening into the abdomen, it is possible to disturb this mechanism: naturally when the gall-bladder or ducts suffer interference the disturbance is greater. Taylor and Wilson<sup>11</sup> noted in their experimental work on dogs that narcosis, cooling and mechanical damage hindered the appearance of what they held to be the normal action of the gall-bladder. Schöndube<sup>12</sup>, Levine<sup>13</sup> and Held and Goldbloom<sup>8</sup> point out how careful one must be in accepting results obtained experimentally where operative measures and general anaesthesia have been employed.

As regards observations made on the human being during operation, caution must be exercised too in assessing the results of these. One has already made reference to Taylor

and Wilson's findings as regards the effects of narcosis, and Kalk<sup>3</sup> refers to the work of Friedenwald, Martindale and Kearny who were able to show how very easily the biliary-tract is disturbed by the use of anaesthesia. In addition, as a rule, morphine or one of its derivatives is administered before operation, and that these substances have definite effects on the biliary-apparatus has been shewn clearly by Schöndube and Lürmann<sup>14</sup>: apparently they produce relaxation of the gall-bladder, thereby interfering with its natural functioning. Reach and Eiger (quoted by Held and Goldbloom<sup>8</sup>) noted that morphine was capable of producing increase of the tone - in some cases amounting to spasm - of the sphincter of Oddi. This shows how carefully the observations made on the human being during operation, with or without general anaesthesia, must be considered before conclusions are drawn.

The investigators who attempted to disprove the theory that the dark bile obtained after the use of certain substances has its origin in the gall-bladder confined themselves almost exclusively to animal experiments. Auster and Crohn<sup>15</sup> and Diamond<sup>16</sup> experimented on dogs and arrived at the conclusion that the gall-bladder plays the part of a reservoir only and has little or no definite function. Kalk<sup>3</sup> was unable in numerous experiments on animals to bring about any outflow of dark bile from the gall-bladder: Bassler, Lockett and Lutz<sup>5</sup> experimented also with animals, and from the results they obtained decided that the gall-bladder has no specific function. These results, because of the conditions under which they were obtained, must, in view of what has been said before, be regarded with a degree of scepticism.

The proofs in favour of the site of the dark bile obtained after the use of various substances being the gall-bladder are conclusive. Pribram<sup>17</sup> and Matsuo<sup>18</sup>, during operations on human beings were able to observe,



after the use of peptone and magnesium sulphate, contractions of the gall-bladder with an outflow from it of dark bile. It is interesting to note that when Pribram gave scopolamine or morphine he failed to obtain any response, on the part of the gall-bladder, to peptone: Matsuo used lumbar-narcosis without morphine or scopolamine and was able to obtain, by the use of magnesium sulphate, bile stained a deep red colour with Azorubin<sup>5</sup> which had been injected some time before (this is a substance which, as is known, is absorbed by the liver and excreted after some time into the gall-bladder).

Certain experiments on animals undertaken under more or less normal physiological conditions are interesting and conclusive, as the faculty of discharging its contents possessed by the gall-bladder was proved radiologically. Boyden (referred to by Held and Goldbloom<sup>8</sup>) used cats in his experiments, performing a preliminary operation during which he emptied the gall-bladder of its contents, replacing them with Lipiodol or Iodipin: after healing had taken place, egg-yolk was administered, or cholin or pituitrin injected, and the subsequent gradual emptying of the gall-bladder was able to be observed by radiological screening and pictures. The contrast material was seen, after 3 minutes, in the cystic duct, after 5 minutes in the common-duct and after 7 minutes in the intestine. Whitaker<sup>19</sup> by means of similar experiments, injecting olive-oil emulsion intravenously, showed radiologically that the gall-bladder does empty definitely, and he was able also to follow the route taken during this by the contents. Hamrick<sup>20</sup> by means similar to Boyden's was able to confirm the latter's results.

Matsuo<sup>18</sup> and Tada and Nakashima<sup>21</sup> experimented on the

human being, filling the gall-bladder with Azorubin S (a colouring-material to which reference has been made before): they passed a tube into the duodenum, magnesium sulphate was introduced thereafter into the duodenum through the tube and deep-red bile, which could have come only from the gall-bladder, was obtained. Kalk<sup>3</sup> mentions that Hatziéganu and Halitza using indigo-carmin instead of Azorubin S were able to repeat the results of Matsuo and Tada and Nakashima, obtaining dark blue-green bile: that this must have come from the gall-bladder is rendered even more probable by the fact that when Hatziéganu and Halitza repeated their experiments in cholecystectomized patients no such dark bile was obtained. Kalk<sup>3</sup> repeated these experiments, using Hypophysin, and his results were similar.

Kalk<sup>3</sup> makes reference to the experiments of Feissly which besides being interesting, are convincing: in these the gall-bladder was filled by means of Tetrabrom or Tetraiod-phenolphthalein (confirmed radiologically), after which a tube was passed into the duodenum and magnesium sulphate administered: dark bile was obtained in which the bromine or iodine content was appreciably increased, the iodine content of the dark bile being indeed 13 times that of the light bile obtained before magnesium sulphate was given.

Numerous workers - amongst them Pribram, Grunenbergr and Strauss<sup>22</sup>, Kaznelson and Reimann<sup>23</sup>, Whitaker<sup>19</sup>, Schiller<sup>24</sup> and Eimer<sup>25</sup> - by means of cholecystography in human beings were able to furnish proof of the ability of the gall-bladder to discharge its contents. They noted a decrease in size of the gall-bladder after the administration of such substances as egg-yolk with cream, Wittepeptone, magnesium sulphate, oil and pituitary extract, showing conclusively that these substances do cause an outflow of the contents of the gall-bladder: they were, in some cases,

able to follow the decrease in the size of the viscus, through its various phases until it was no longer visible. Apparently of all substances as yet used to induce a flow of dark bile - whether it be from the gall-bladder or no (most investigators agree however that it is) - that suggested and used by Boyden (quoted by Held and Goldbloom<sup>8</sup>) i.e. egg-yolk with cream seems the most reliable and effective. (The writer has been able to confirm the effect of egg-yolk and cream in reducing the size of the "contrast-filled" gall-bladder).

It is worthy of mention that Kalk<sup>3</sup> found that the dark bile obtained by means of his double-tube (to which further reference will be made later) after the injection of hypophysin was in close agreement, as regards pigment-content, with that which he obtained later at operation from the same cases. One might make reference also to the finding of Typhoid bacilli in increased numbers in the dark bile obtained by duodenal catheterization: this was achieved by Stepp<sup>26</sup> who found no or very few bacilli in the light bile but numerous bacilli in the reflex dark bile, obtained after the administration of peptone: one knows that in certain cases the gall-bladder is ~~often~~ the seat of such bacilli in numbers.

Concluding this discussion one may say justifiably that the proofs in favour of the gall-bladder's being the site of the dark bile obtained by the use of various cholekinetic substances are definite and conclusive. Many workers have, in addition, shown that in cases where the gall-bladder is not capable of functioning properly e.g. cystic duct blocked by stone: atrophied gall-bladder, it is impossible to obtain any dark bile.

One might here make short reference to a matter which has, in the past, caused controversy i.e. by what route does

the gall-bladder empty? It has apparently always been admitted that the gall-bladder is filled via the cystic duct, but Sweet, Halpert and Blond (referred to by Kalk<sup>3</sup>), as the result of their experimental work, denied that this viscus empties over the cystic duct: they suggested that the bile passes from the gall-bladder by the lymph and blood-vessels and regarded the absorption-function as the only one possessed by that organ. The evidence against these views is overwhelming and it will suffice to adduce only one or two proofs. Copher (quoted by Graham<sup>27</sup>) tied the cystic duct in animal-experiment and then filled the gall-bladder with dye, finding that the dye remained in the gall-bladder so long as the cystic-duct was ligated: Held and Goldbloom<sup>8</sup> refer, in this connection, to the work of Whitaker and Maddock who repeated the experiment made by Copher with similar results. Boyden, Hamrick<sup>20</sup> and Whitaker<sup>19</sup>, by means of radiological investigations of the gall-bladder (previously filled with contrast-substance) were able to follow the passage of the contrast-substance along the cystic duct into the common-duct and intestine. Berg<sup>28</sup> was able to observe radiologically, making repeated pictures, stones passing from the gall-bladder into the cystic duct. In addition the fact that, at operation, stones are often found in the common-duct, at times in the intestine, and in other cases in the stools is proof that the gall-bladder empties via the cystic duct. One sees therefore that there cannot be any doubt regarding the part played by the cystic duct in the emptying of the gall-bladder and that the theories of Sweet and Halpert and Blond are untenable.

PROOF OF CONTRACTILE POWER OF GALL-BLADDER.

It is proposed to consider now the question whether the gall-bladder is capable of contracting actively or no: this is again a subject about which there has been, for many years, much discussion and varying opinion.

Winkelstein<sup>29</sup> opposed the view that the gall-bladder, during the discharge of its contents, contracted actively, arriving at this conclusion by means of animal-experiments: he sewed small silver plates to the serosa of the gall-bladder and during screening (X-ray) he was unable, after the administration of food, magnesium sulphate or decinormal hydrochloric acid, to observe any marked change as regards the position of the platelets: had there been any active contractions, he held, the platelets would have been drawn together after the ingestion of food, etc. Only slight movements were noted which were synchronous with respiration. In view of these findings, he inclined to the view that emptying of the gall-bladder is passive and gradual, depending on pressure changes in the abdomen produced by respiration.

By reason of his own experience and that of his fellow-workers Graham<sup>27 & 30</sup> came to a similar conclusion i.e. that the emptying of the gall-bladder is a passive process: in animals and in the human being at operation, ~~he held~~, electrical stimulation which was sufficient to cause contraction of the bowel and urinary bladder was unable to produce this effect on the gall-bladder: nor was mechanical stimulation productive of contraction in this viscus. In another experiment done by his fellow-workers, the gall-bladder was replaced by a small rubber bag: thereafter Tetraiodphenolphthalein was injected intravenously, and the bag was observed to fill and to empty, although a little more slowly than normally. Graham was unable, at any time

during operation on the human being, to observe contraction of the gall-bladder. He admitted that the viscus is capable of emptying but denied that it possesses any contractile power, holding that the emptying is passive and dependent on elastic recoil and the fall in pressure, occurring in the common-duct, when the sphincter of Oddi opens: this takes place, according to him, as a result of changes in the tone of the duodenal wall which are brought about possibly by such substances as magnesium sulphate. Burget<sup>31</sup> also regarded duodenal peristalsis as an important factor in the emptying of the gall-bladder, supporting the view that intra-abdominal pressure and the tonicity and peristaltic action of the duodenum are the important factors producing expulsion of gall-bladder contents.

Haberland<sup>32</sup> also opposed the view that the gall-bladder during emptying was the seat of active contractions. He experimented on animals and was unable, at any time during laparotomies on them, to observe active contraction of the gall-bladder after magnesium sulphate had been introduced into the duodenum: nor was he able to cause contraction of this viscus by using pituitrin, pilocarpine, electrical stimulation of vagus and sympathetic nerves, nor by the use of direct electrical stimulation applied to the organ, although by this means he was able to produce marked contraction of the bowel. He failed also, during laparotomy on patients, to produce by direct electrical stimulation any contraction of the gall-bladder and, in addition, never noted at any time during operation any spontaneous movement on the part of this organ. As the result of his findings he decided that the expulsion of gall-bladder contents takes place passively during inspiration as a result of descent of the diaphragm and "milking" action of the duodenum: he emphasised the fact that the position of the gall-bladder with regard to the

liver, i.e. its being embedded to such a degree, precludes any active contractile movement of this viscus. Held and Goldbloom<sup>8</sup> refer to Carlson, the noted physiologist, who, as a result of his experimental work, arrived at the conclusion that neither the gall-bladder nor the sphincter of Oddi has any special function but that the passage of bile from the gall-bladder is dependent on the tone and periodic contractions of the duodenum.

With regard to the above-mentioned experimental results and also to those which follow, one must keep in mind what has been said before concerning the assessment of such results.

On the other hand some of the earliest experimental work on animals produced proof of the active contractibility of the gall-bladder: in this regard the work of Doyon (quoted by Kalk<sup>3</sup>) and Bainbridge and Dale<sup>33</sup> may be mentioned. They introduced an air-balloon into the gall-bladder for the purpose of estimating pressure changes in the organ and were convinced from their findings that contraction took place. Bainbridge and Dale, as a result of their work, came to the conclusion that the vagus supplies motor nerves to the gall-bladder and that by stimulation of this nerve it is possible to produce an increase of tone and rhythm of this organ. Doyon observed in various experiments, after electrical stimulation, definite contractions of the gall-bladder: he was able to clarify the knowledge of <sup>the</sup> detailed nervous action of the organ and shewed that stimulation of the peripheral end of the splanchnic nerve caused major contraction together with contraction of the sphincter of Oddi, whereas stimulation of the central end of this nerve produced relaxation of the gall-bladder and of the sphincter of Oddi: stimulation of the central end of

the vagus caused contraction of the organ with relaxation of the sphincter of Oddi, and peripheral stimulation of this nerve was without effect. Held and Goldbloom<sup>8</sup> refer to the experimental work of Westphal who, after stimulation of the vagus, observed hyper~~tonus~~<sup>t</sup>onus of the gall-bladder, whereas sympathetic stimulation produced atony: they refer also to Eiger who in his experiments, by stimulating the vagus, noted an increase in the bile flow from the gall-bladder.

One might here mention shortly that consideration of the anatomy of the gall-bladder would lead one to presume that it is capable of active contraction. The wall is rich in smooth-muscle and poor in elastic fibres: if contraction were not an important function of the organ, one would expect a preponderance of elastic fibres. In addition the gall-bladder has an important nerve supply from the vegetative system, and one would expect that an organ so well endowed with nerves and musculature would have an active function.

Stepp and Düttmann<sup>9</sup> who used dogs (with open abdomens) in their experiments observed frequently, after the introduction of Wittepeptone into the duodenum, strong ring-shaped contractions travelling from the fundus of the gall-bladder in the direction of the cystic duct together with expulsion of the contents of the organ: they obtained similar results using magnesium sulphate, oil, etc. Kalk<sup>3</sup>, working with Schöndube, noted also, in animal experiments, contraction of the gall-bladder after the use of oil, hypophysin and pilocarpine.

Various experiments were undertaken in animals during which the pressure in the gall-bladder during its active phase was measured, in order to discover if any deductions as regards the occurrence of active contractile movements could be drawn from them.



Kalk<sup>3</sup>, working with Westphal and Schöndube, undertook experiments similar to those of Haberland, using cats and rabbits: they ligated the hepatic duct while the cystic duct was clamped, and vagal stimulation by means of pilocarpine caused a definite pressure increase in the gall-bladder (into which a manometer had been inserted). It is obvious that contractile movements on the part of the gall-bladder were necessary to produce this rise in pressure, for the clamping of the cystic duct prevented any effect being exercised on the organ by duodenal peristalsis: in addition, during these experiments, the neighbouring organs were kept clear of the gall-bladder in order to obviate their having any effect on the viscus. Higgins and Mann<sup>34</sup>, using dogs in which local anaesthesia was employed, ligated the hepatic duct and measured the pressure in the common duct: they found, after the administration of egg-yolk and cream, an extraordinary rise in pressure which they regarded as explicable only by active contraction on the part of the gall-bladder. Kalk<sup>3</sup> refers to animal experiments undertaken by Brugsch and Horsters in which a marked increase in pressure in the gall-bladder, together with expulsion of the contents of the organ, was observed after the use of histamine. Westphal and Schöndube<sup>35</sup> tied, in animals, the hepatic duct, at the same time clamping the cystic duct: after injecting bilirubin into the gall-bladder they observed, when certain substances had been passed into the duodenum, a definite rise of pressure in the bladder. McMaster and Elmann (quoted by Kalk<sup>3</sup>) employed local anaesthesia in their animal experiments and, having made an ingenious fistula, measured the pressure in the gall-bladder, common and hepatic ducts: they noted, after the ingestion of food, a marked increase in pressure in the gall-bladder, an occurrence which, according to the

conditions of their experiments, could be explained only by active and forcible contraction of this organ.

The experiments undertaken by Whitaker<sup>19</sup>, to which reference has been made before, are important: using cats and dogs he rendered the gall-bladder visible - radiologically - by injecting intravenously Tetraiodophenolphthalein, in most cases however filling the organ by direct puncture with iodized oil: the abdomen was then closed, and after healing had taken place olive oil emulsion was either administered per os or injected intravenously, and the resultant emptying of the gall-bladder followed by screening and pictures. It was observed that emptying was complete - an occurrence which Whitaker held could be due only to active contraction of the viscus and certainly not to elasticity alone. It is worthy of special mention that in these experiments retrograde filling of the hepatic duct was noted. Pituitrin and barium chloride produced also discharge of gall-bladder contents. Whitaker, as the result of these experiments, took the view that the contents of the gall-bladder are expelled by the activity of the musculature of the organ and that this is independent of respiration, duodenal peristalsis and sphincter control, an opinion which is directly opposed to those of Haberland and Graham.

Higgins and Mann<sup>34</sup> conducted experiments which are convincing: they selected for their work pike, in which neither diaphragm- nor abdominal wall-movement is present, and were able to show that after the administration of egg-yolk and cream emptying of the gall-bladder took place - a result explicable only - because of the type of fish selected for experiment - by contractile movement of the viscus. In other experiments on guineapigs the gall-bladder was - under local anaesthesia - placed outside the abdominal wall, and definite contractions of the organ with decrease in its size were observed after egg-yolk and cream had been given (it is interesting to note, in view of what has been said before

regarding the effects of general narcosis, that when this, i.e. general narcosis, was employed Higgins and Mann were unable to observe that egg-yolk and cream had any effect on the gall-bladder).

Held and Goldbloom<sup>8</sup> refer to experiments of Boyden in which he severed the gall-bladder from the duodenum and noted that the response of the organ to food was exactly as before this had been done i.e. emptying took place: this result certainly speaks against duodenal activity being responsible for the discharge of contents from the gall-bladder. Held and Goldbloom<sup>8</sup> regard the duodenal suction theory (as explanatory of gall-bladder emptying) as absurd: the rapidity of emptying of the organ, they hold, is dependent on the type of food taken, and the fact that carbohydrates do not produce such an outflow of bile from the gall-bladder as do fats is, in their opinion, against the view that duodenal action plays an important part in the emptying of the viscus. They point out also that hunger causes definite contractions of stomach and duodenum and yet, in hunger, no emptying of the gall-bladder takes place, the organ remaining full.

Held and Goldbloom<sup>8</sup> emphasise also that in numerous cases where the right side of the diaphragm is immobile because of pleurodiaphragmatic adhesions, acute infections of the right pleura, traumatic paralysis of the diaphragm due to injury or sub-diaphragmatic abscess emptying of the gall-bladder takes place: they regard this as being definitely against the idea that respiration plays any important part in the discharge of contents from the gall-bladder. Hamrick<sup>20</sup> also holds the view, as the result of his experimental work, that respiratory movements as well as changes in extra- and intra-abdominal pressure play only a minor part in the emptying of the gall-bladder: he mentions that spontaneous ejaculation

of at least a little bile from the organ may be produced by the introduction of a tube into the duodenum, or by filling the stomach with air, but that one never sees even such a partial emptying as this produced by the usual changes in intra- and extra-abdominal pressure.

It is proposed now to make short reference to experiments which were undertaken on the isolated gall-bladder. Lieb and MacWorther (quoted by Kalk<sup>3</sup>) were the first to attempt such experiments and observed contractions of the isolated gall-bladder of the dog after the use of chlorbarium, physostigmine, strophanthin and pilocarpine. Chiray and Pavel<sup>36</sup> undertook similar experiments, immersing the isolated bladder in Ringer's solution to which  $\frac{1}{3}$  defibrinated blood had been added: the movements of the organ were registered kymographically, and the occurrence of definite contractions was shown. Experimenting also with the isolated gall-bladder, Ischiyama (referred to by Kalk<sup>3</sup>) observed automatic movements: barium chloride, physostigmine and pilocarpine caused increase in the tone of the isolated bladder while atropine and scopolamine lessened this: choline increased the automatic movements of the organ. Kalk<sup>3</sup> refers to similar experiments made by Brugsch and Horsters: they noted that acetylcholin, pilocarpine and histamine brought about contractions of the gall-bladder, these taking place both longitudinally and circularly, the former being the greater. Erbsen and Damm<sup>37</sup> repeated later Brugsch and Hosters' experiments on the isolated gall-bladders of guineapigs and agreed that histamine and pilocarpine cause contractions of the organ; they noted also that these took place in the longitudinal and circular axes, the contractions in the former being the greater. Erbsen and Damm observed also that the action of pituitrin

on the isolated gall-bladder seemed to depend on the pressure in the organ; when it was contracted, or empty or only partially filled, pituitrin caused relaxation, whereas when it was full a definite increase in tone was observed after the use of this drug. The experiments of Kalk<sup>3</sup> on the isolated gall-bladder proved also that the organ possesses the faculty of active contraction. Thus experiments undertaken on the isolated gall-bladder seem to prove conclusively that the viscus is capable of contracting actively.

Graham<sup>27</sup> comments on the fact that no one appears to have been able to observe contractions of the gall-bladder during operation on the human being: admittedly these have been seldom noted - they have however been seen - but this is easily explained when one remembers the remarks made earlier regarding the effect of general narcosis and morphine derivatives on gall-bladder function. Pribram<sup>17</sup>, Matsuo<sup>18</sup> and Moser (referred to by Held and Goldbloom<sup>8</sup>) did observe such movements on the part of the organ during operation: in these cases morphine and in some of them general anaesthesia were not employed.

One comes now to proofs of gall-bladder contractibility which are free of the objections which can be levelled at results obtained in animal-experiment and in human beings during operation: one refers to radiological evidence. The writer saw in Berlin a series of X-ray pictures made by Berg which are, in this connection, interesting and convincing. The pictures were taken in a case where numerous stones were seen in the gall-bladder (without contrast-filling): the first plate showed these clumped together, i.e. in circular arrangement. 2cc. pituitrin were injected (pictures being made at intervals after this), and it was striking to observe how the arrangement of the stones altered: instead of lying clumped together, as they did

before pituitrin was given, they assumed a columnar form, i.e. one lying behind the other, some finding their way into the region of the neck of the gall-bladder. During a spontaneous attack of colic pictures were again made, and again the circular arrangement of the stones gave place to a longitudinal one: this was however not so marked as in the first series of plates, made after the injection of pituitrin. Such an occurrence can be explained only by active contractile movements of the gall-bladder. Kalk<sup>3</sup> noted that amongst Whitaker's X-ray pictures (made using contrast-filling) there was one which, after the ingestion of fat, showed the stones pressed together, due presumably to contraction of the gall-bladder wall. Held and Goldbloom<sup>8</sup> confirmed Brunner's results and were able to show radiologically - using Tetraiodphenolphthalein - that the stones in the gall-bladder assumed a different position after the ingestion of a fat-meal.

That cholecystographic proof of contractile power on the part of the gall-bladder is not obtained easily is emphasised by Held and Goldbloom<sup>8</sup>: as they point out, two-thirds of the organ is embedded in the liver, and it is therefore difficult to see its movements: in addition - as shown by the experimental work of Brugsch and Horsters and Erbsen and Damm<sup>37</sup> - the gall-bladder contracts chiefly in the longitudinal axis and, where longitudinal muscle predominates, contractions are seldom visible as peristaltic waves (the same applies to the urinary bladder, fundus and lesser curvature of the stomach, and yet these undoubtedly contract). In spite, however, of these difficulties cholecystographic proof of gall-bladder contraction has been adduced. Kalk<sup>3</sup> refers to X-ray pictures made by Schöndube: the gall-bladder had been filled with contrast material and

after the introduction of oil into the duodenum, a tonic contraction of the organ was observed, synchronous with the appearance of dark bile (obtained by tube): a gradual filling of the ducts by contrast material was noted, and in addition the hepatic duct was filled. This tonic contraction, together with retrograde filling, presents quite definite proof of the power of the gall-bladder to contract. Levine<sup>13</sup> and Held and Goldbloom<sup>8</sup> also observed - fluoroscopically - definite contraction of this organ. Kalk<sup>3</sup> holds that Boyden's cholecystographic investigations are such that no doubt can exist regarding the ability of the gall-bladder to contract: Held and Goldbloom<sup>8</sup> refer also to the observations made by Boyden: his pictures showed the gall-bladder in the process of emptying, narrowing of the fundus being seen at first and definite contractions later. X-ray pictures which showed the gall-bladder contracting were made also by Held and Goldbloom<sup>8</sup> themselves: hour-glass contractions and indentations in the wall were seen.

That stones leave the gall-bladder and pass through the narrow cystic duct - being at times impacted there - no one can deny. Whitaker<sup>38</sup> inserted stones into the gall-bladders of animals and was able to follow their passage after the administration of a fat-meal: they became impacted. One cannot explain the passage of stones otherwise than by forcible muscular contraction of the gall-bladder.

Finally one may make short reference to laparoscopic proof of active contractibility of the gall-bladder. Kalk<sup>39</sup> has observed, during such an examination, contraction of the gall-bladder, and the writer has also seen contraction of this organ take place, during laparoscopy, after egg-yolk and cream had been administered.

In conclusion, one must say that the proofs in favour of the gall-bladder's possessing active contractile power are definite and conclusive: these proofs show clearly that it is impossible to agree with the views of those investigators who hold that the emptying of the gall-bladder is caused chiefly by respiratory pressure-changes, duodenal peristalsis, and the elasticity of the organ.

#### PITUITARY EXTRACTS AND OIL AS CHOLEKINETIC AGENTS.

As mentioned earlier it is proposed in these investigations to follow, more or less, the technique employed by Kalk: he used, as cholekinetic agents, pituitary extracts and olive oil, laying particular stress on the value of the former: only if he failed to obtain response, i.e. emptying of gall-bladder with pituitrin etc., did he make use of oil. It might be well to produce proof that both these substances are capable of causing the gall-bladder to contract and expel its contents. The effectiveness of most of the other substances used for this purpose has been confirmed by various investigators: the value of magnesium sulphate, the substance most commonly employed in biliary drainage, has been confirmed by Lyon<sup>2</sup> & <sup>40</sup>, Tada and Nakashima<sup>21</sup>, Pribram<sup>17</sup>, Matsuo<sup>18</sup>, Hollander<sup>41</sup>, Howard<sup>42</sup>, Taylor and Wilson<sup>11</sup>, Hurst<sup>43</sup>, Held and Goldbloom<sup>8</sup> and Dicks<sup>10</sup>: the value of peptone has been clearly demonstrated by Stepp particularly and also by Held and Goldbloom<sup>8</sup>, and that of a meal with high fat content by Whitaker<sup>19</sup>, Held and Goldbloom<sup>8</sup>, but especially by Boyden.



According to Kalk<sup>3</sup>, Rost, Klee and Klüpfel were the first to employ oil, in animal experiments, for the purpose of producing emptying of the gall-bladder. Diachowski and Rachlin (quoted by Kalk<sup>3</sup>) and Stepp and Düttmann<sup>9</sup> by reason of their investigations concluded that oil is definitely capable of bringing about gall-bladder contraction with expulsion of the contents. It is worthy of note that Whitaker<sup>19</sup> in his animal-experiments, found that olive oil emulsion, given intravenously, was effective in this regard. Kalk<sup>3</sup> found that oil has a definite and marked cholekinetic action, and finally Held and Goldbloom<sup>8</sup> also proved its efficacy in biliary drainage.

Pituitary extracts have been employed as cholekinetic agents by a number of investigators. Houssay (referred to by Kalk<sup>3</sup>) while engaged in experiments in dogs in 1911 observed, after hypophysin had been injected, increase in the tone of the gall-bladder and contractions. Kalk and Schön-dube<sup>44</sup> during investigations on the stomach, using the double-tube (to which fuller reference will be made later) and hypophysin, were struck by the fact that, shortly after the injection, they obtained dark bile through the tube which lay in the duodenum. Since then Kalk<sup>3</sup> has used pituitary extracts continuously and is convinced they are not only capable of producing expulsion of gall-bladder contents but that they are the most effective of all substances used so far for this purpose. Adlersberg (quoted by Held and Goldbloom<sup>8</sup>), while studying the working of chloretone and other narcotics, observed that, when chloretone was injected some time before pituitrin was given, the action of the latter was hindered, and no gall-bladder emptying took place. As chloretone has a paralytic action on the base of the brain, Adlersberg concluded that pituitrin

exercises its influence on the gall-bladder through the central nervous system - particularly the base of the brain: obviously he regarded pituitrin as a drug capable of causing contraction of the gall-bladder.

Since the publication of Kalk and Schöndube's observations numerous investigators have been able to confirm their findings i.e. as regards pituitary extracts being capable of producing emptying of the gall-bladder. Berg<sup>25</sup> found radiologically that pituitrin caused a definite decrease in the size of the organ and formed the opinion that it has a more powerful kinetic action on the gall-bladder than magnesium sulphate. Verification of Kalk and Schöndube's findings was made by Pribram, Grunenberg and Strauss<sup>22</sup> and Kaznelson and Reimann<sup>23</sup>: using contrast-filling of the gall-bladder, they were able radiologically to note decrease in the size of the organ and diminution in the degree of opaqueness of the shadow after hypophysin had been injected. Held and Goldbloom<sup>8</sup> mention that Sösmann, Whitaker and Edson by similar means observed, after pituitrin, emptying of the gall-bladder. Feissly and Saralequi (quoted by Kalk<sup>3</sup>) confirmed these findings and commented on the powerful action of pituitrin on the organ. Cholecystography was employed also by Eimer<sup>25</sup> and he too noted definite contraction of the gall-bladder, with the appearance of flat waves in the wall, after the injection of pituitrin. Kalk<sup>3</sup> mentions that Boyden, in his animal experiments where the gall-bladder was filled with Lipiodol or Iodipin, observed, after pituitrin, contraction of the viscus. Numerous other investigators, e.g. Schiller<sup>24</sup>, Pennetti<sup>45</sup>, were able also to confirm the opinion originally expressed by Kalk and Schöndube that pituitary extracts are capable of causing contraction of the gall-bladder and expulsion of

its contents. Incidentally Kalk<sup>3</sup>, experimenting on the isolated gall-bladder of the guineapig, observed marked contraction after hypophysin.

A few investigators that employed pituitary extracts found themselves unable to confirm Kalk and Schöndube's views as regards their effect on the gall-bladder. Haberland<sup>32</sup> and Brugsch and Horsters (referred to by Kalk<sup>3</sup>) denied that these drugs act cholekinetically on the organ. Haberland was unable to observe any contraction of the gall-bladder at operation after the injection of hypophysin, although marked bowel contraction was clearly visible: it is interesting to note that he found magnesium sulphate under similar circumstances also to be without effect on the gall-bladder. Brugsch and Horsters, experimenting with animals, did observe <sup>the</sup> outflow of dark bile after pituitrin, but this they attributed not to contraction of the gall-bladder but to relaxation followed by passive outflow of the contents. This is mechanically difficult to understand: the valve arrangement of the cystic duct is such as would prevent the passive outflow of the contents from the gall-bladder, and while the organ is relaxed one would expect bile rather to enter it from the hepatic duct than to flow from it. In addition relaxation of the gall-bladder after the use of pituitary extracts was certainly not observed by those investigators who made use of radiology in their observations. If relaxation takes place after pituitrin and other pituitary extracts, the gall-bladder would be the only organ with smooth muscle which reacts in this way: all other organs with smooth muscle, e.g. stomach, bowel, uterus, etc., contract after

the use of these substances. Brugsch and Horsters used animals for their experiments, and Kalk<sup>3</sup>, in numerous experiments in dogs and cats in which he opened the abdomen, very seldom noted gall-bladder contractions, a finding which he attributes to disturbance of the innervation of the organ and the unphysiological conditions produced by operative interference and narcosis.

Bernstein and Held<sup>46</sup> were unable, in 17 out of 18 cases investigated, to obtain dark bile by means of the duodenal tube (nor to observe any decrease in the size of the gall-bladder) after the injection of 2 cc. pituitrin. Kalk<sup>3</sup> answers this by suggesting that the pituitary preparation used by them had degenerated, i.e. lost its potency, or that the tube did not lie in the duodenum. The reply of Held and Goldbloom<sup>8</sup> is interesting: they insist that the tube, in these cases, was without doubt in the duodenum and produce X-ray pictures to confirm this. They do however admit, probably as the result of further investigations, that pituitrin can cause expulsion of the contents of the gall-bladder, although not so frequently as Kalk would have it.

The weight of evidence is definitely in favour of pituitary extracts being substances capable of producing gall-bladder contraction with expression of the contents: one may therefore employ it with confidence in biliary drainage as an aid to the diagnosis of gall-bladder disease: the same applies to oil.

It would be well to mention the reasons which prompted Kalk to select pituitary extracts and oil, particularly the former, for use in biliary drainage with a view to obtaining assistance in the diagnosis of gall-bladder disease. Both magnesium sulphate and Wittepeptone are

substances possessing not only cholekinetic but also chloreretic properties, i.e. they induce a flow of bile from the liver as well as from the gall-bladder: this chloreretic effect of these two substances has been shown by Stransky (quoted by Kalk<sup>3</sup>). As has been demonstrated by some investigators, the liver has a definite concentrating power which is of course, excepting in certain cases, e.g. pernicious anaemia, not nearly so well marked as that of the gall-bladder: when dark bile is obtained after the use of magnesium sulphate and Wittepeptone some difficulty might arise in deciding what is liver bile and what comes from the gall-bladder. In addition the factor of dilution has to be taken into account after the use of such substances, the increased flow of liver-bile producing some dilution of the bile expressed from the gall-bladder with consequent decrease in the pigment content. Pituitary extracts and oil are only cholekinetic in action producing no choleresis: proof of this as regards the former has been adduced by Erbsen and Damm and as regards the latter by Stransky (both quoted by Kalk<sup>3</sup>). Kalk holds that pituitary extracts if given in sufficient quantities have a more marked action on the gall-bladder than magnesium sulphate and peptone. Pituitary extracts have, in addition, another marked advantage over these two other substances - and for that matter over oil - i.e. they are injected hypodermically: therefore when dark bile is obtained from the gall-bladder it is not diluted as is the case with magnesium sulphate and peptone which are introduced directly into the duodenum, remaining there for some time. This is particularly valuable as regards the obtaining of accurate results in the estimation of the pigment content of the gall-bladder bile upon which Kalk lays particular diagnostic worth. Lastly Kalk regards

pituitary extracts as being definitely more reliable in their action than magnesium sulphate, again presuming that sufficient is used and the particular preparation a good one. While Stepp and others seem to have no doubts concerning the reliability of peptone, Langanke (referred to by Kalk<sup>3</sup>) regards it as quite unreliable. Lyon and those investigators who employed magnesium sulphate are apparently well satisfied with it, but Kalk, who has had long experience with this substance, regards it as definitely less reliable in its effect on the gall-bladder than pituitary extracts: he noted that the bile obtained with it from the organ was of a comparatively low concentration and held this was not truly indicative of the condition of the gall-bladder as regards concentration-ability. He makes no attempt however to explain in how far this was due to dilution produced by the bile secreted from the liver as a result of the chloreretic action of magnesium sulphate. Kalk<sup>3</sup> remarks that the experiences of Chabrot, Etann and Gambillard with magnesium sulphate were not good: they found that in 50% of their normal cases it was incapable of producing any response on the part of the gall-bladder. It can be seen from this that magnesium sulphate and peptone, especially the former, are not absolutely reliable cholekinetic agents, while Kalk regards pituitary extracts as definitely superior in this regard. One must however remember at this juncture the opinions of Held and Goldbloom<sup>8</sup> who regard pituitrin as being not a quite reliable cholekinetic substance.

Oil has of course not all the advantages claimed by Kalk for pituitary extracts: that it is capable of producing marked contraction and emptying of the gall-bladder

has already been shown: in addition it is a purely cholekinetic substance, having no choleric properties. Its use however in biliary drainage presents difficulties in the estimation of the pigment-content of bile obtained from the gall-bladder and in the microscopic examination of the sediment, fat-globules obscuring the other constituents. Kalk of course prefers pituitary extracts to oil in duodenal catheterization.

Therefore if what Kalk holds as regards the potency of pituitary extracts in its action on the gall-bladder and above all as regards its reliability is true it is obvious that these should be the substances of choice in biliary drainage, having definite advantages over all other substances used in this test: it is clear also that of these other cholekinetic agents oil is to be preferred.

#### GENERAL TECHNIQUE EMPLOYED IN PRESENT INVESTIGATIONS.

Kalk<sup>3</sup> used in his cases a double-tube: one tube was introduced into the duodenum, the other into the stomach, and both were connected to an elaborate water-suction apparatus which was provided with a manometer to allow of the pressure exerted being measured and kept uniform: bile was sucked back into a glass cylinder while at the same time stomach contents were sucked back into a similar cylinder, the bile being thus kept clear of stomach contents. Such a method has obviously much to commend it, the bile being obtained in a more or less

pure state, and its examination thus rendered accurate. The apparatus is however expensive and demands, when in use, constant attention, the whole procedure being practicable only when one can devote considerable time to it. In view of these difficulties in this series of cases only one tube was used, being passed into the duodenum (no suction-apparatus was employed). In addition Kalk preferred to repeat the intubation two or three times in each case: one must admit that, as with all tests, the oftener biliary drainage can be repeated in a given case the more valuable and reliable are the results. One found however early on in the investigations that the patients were exhausted after the test, and one did not want to repeat it: Dicks<sup>10</sup> and Hurst<sup>47</sup> amongst others hold that duodenal intubation is by no means disturbing to the patients: one doubts this while admitting that the test as applied by these investigators did not last so long as it did in this series. To prevent undue disturbance of the patients the test was employed therefore in these investigations only once in each case. Kalk estimated the amount, colour and bilirubin content of the bile in his cases: in this series no attention was paid to the amount of bile obtained immediately after intubation nor to that obtained from the gall-bladder, as it was seen after a few cases had been investigated that nothing could be deduced from this, the quantities being so variable. Lyon<sup>48</sup> showed that the amount of bile entering the intestine in the course of a day is extremely variable, and Loeber<sup>49</sup> noted, in 123 cases, that the quantity of bile obtainable from the gall-bladder showed marked variations but was unable to attach any significance to these.



No particular attention was paid, in these investigations, to minor differences in the colour of the bile, only marked differences being held worthy of note. Lyon<sup>2</sup> laid stress on 3 types of bile, typed as regards colour and origin: he divided the bile obtained by duodenal catheterization into 3 classes:- A - bile, i.e. light bile obtained at once on intubation: this he held to be duct-bile: B - bile, i.e. dark bile from the gall-bladder obtained after the introduction of magnesium sulphate: C - bile, i.e. light bile coming from liver. This division strikes one as being somewhat artificial and unnecessarily detailed: the bile first obtained on intubation represents obviously the contents of the common duct, but if the flow be allowed to continue it lasts indefinitely, showing that it is, in reality, bile from the liver which is "held up" in the common duct without undergoing there any marked change. The origin of the so-called B - bile is obvious, as is shown by its concentration, and according to the experience of the writer, the so-called C - bile is really similar to the bile obtained immediately on intubation. One noted when the gall-bladder reacted with the expulsion of its dark contents a definite sequence, i.e. as regards the colour of the bile obtained: light bile was obtained through the tube until some time after the giving of the cholekinetic substance, when the bile became suddenly dark in colour and remained so for a period; thereafter it became gradually lighter until finally a continuous flow of light bile, indistinguishable in colour from the first bile obtained, took place. In view of this one regards the classification into A, B and C biles as artificial and unnecessarily detailed, there being, in fact, only two types of bile obtainable by duodenal

catheterization, i.e. bile from the liver and bile from the gall-bladder. Kalk makes nowhere mention of the so-called A, B and C biles, dividing the bile obtained in biliary drainage into liver (light) and gall-bladder (dark) bile.

Kalk<sup>3</sup> lays particular stress on the value of estimating the bilirubin content of the bile as a means of obtaining accurate knowledge of the ability of the gall-bladder to concentrate bile and therefore of its function in this sphere. One agrees that such a method is more accurate than, and has therefore advantages over, the usual visual method which gives, of necessity, only an approximate indication of the concentrating power of the organ. Hollander<sup>41</sup> used a colorimetric method in his work, but this allowed of only rough comparisons being made: Jones<sup>50</sup> employed a spectroscope in his estimations of the pigment content of the bile. The bilirubin content of the bile was estimated in these investigations by means of the Hijmanns van den Bergh colorimeter (manufactured by Hellige, Freiberg i/Br.): the bile is diluted with water to reduce it to a very light yellow colour, and .5 cc. of this is put into the trough, followed by 1 cc. alcohol (96%) and .25 cc. Ehrlich's reagent. The colours of the contents of the trough and the standard wedge are matched, and from the chart provided by Hellige the amount of bilirubin (in milligrams) is obtained: this result is multiplied by 200 (to obtain the percentage value, as only .5 cc. bile was used) and again by the dilution factor. This estimation was made in this series - as advised by Kalk<sup>3</sup> - in only two specimens of bile, i.e. in the lightest obtained before pituitrin and in the darkest bile, if any dark bile had been obtained, after pituitrin and/or oil.

Pituitrin (Parke, Davis), a reliable preparation, was used in most cases, British Drug Houses pituitrin, another reliable preparation, being employed in the others. Portions of the contents of three tubes containing the darkest bile (if any) obtained after pituitrin and/or oil were centrifuged, and the resultant sediment examined microscopically. In addition the bilirubin content of the blood-serum was estimated colorimetrically in those pathological cases where it was possible to obtain blood for this purpose.

#### PARTICULAR TECHNIQUE.

The patients receive no food after 8 p.m. on previous evening, the test being commenced at 9 a.m. on the morning following; this ensures that the gall-bladder is full of bile. Blood is taken from a vein in order that the amount of bilirubin in the serum may be estimated. A special tube is used, slightly less in diameter than the usual Einhorn tube and longer: this tube has a special olive-shaped and perforated metal ending, this possessing the presumable advantages that by its weight it finds its way through the pylorus more easily than the ordinary fractional test-meal tube and that the metal ending provides something for the pylorus to contract on and insinuate into the duodenum. The tube has three markings, i.e. one at 45 cm., one at 60 cm., and one at 72 cm. from the metal bulb: these are the average

distances from the teeth to the fundus of the stomach, to the pylorus and to the ampulla of Vater respectively. The tube is swallowed quickly by the patient to the first marking and then slowly to the 60 cm. marking, fully 20 minutes being taken to reach this latter spot: the reason for the slow swallowing of this part of the tube is to obviate any possibility of producing spasm of the pylorus, which would hinder the later passage of the tube into the duodenum, by the sudden impinging of the tube on the pyloric sphincter region. When the tube is at the pyloric-mark the patient is turned on the right side and the foot of the bed raised by blocks to assist in the entry of the tube into the duodenum: the patient is then instructed to swallow the tube - again slowly (further 20 minutes being taken) - to the 72 cm. marking: slow swallowing of this part of the tube is advisable to prevent, if possible, coiling of the tube in the stomach and to allow of the metal end being insinuated gently into the duodenum.

The passage of the tube through the pyloric sphincter is not always a matter of a few minutes - on the contrary it may take hours: in these investigations one waited at the most 2 hours (having withdrawn the tube to the 60 cm. marking once or twice and having given 60 gr. sodium bicarbonate to release possible pyloric spasm), and if after that period the duodenum had not been entered, it was found advisable, in the interests of the patient, to interrupt the test and repeat it later. In a few cases it was necessary to repeat the attempt twice before the tube found its way into the duodenum. Some investigators do not seem to realise the difficulty associated at times with the passage of the tube into the duodenum: Hurst<sup>51</sup> and Erasmus<sup>52</sup>

amongst others imply that this takes place without any difficulty. On the other hand Lyon<sup>2</sup>, Dicks<sup>10</sup> and Hunt<sup>53</sup> have realised this possible difficulty and advocate the injection of atropine subcutaneously to aid relaxation of the pyloric sphincter (spasm of which is presumably the reason for the non-passing of the tube into the duodenum). One admits that this drug would probably be of assistance in this connection, but the gall-bladder also would be relaxed by it, with the result that the cholekinetic agent given afterwards to cause emptying of this organ might be without effect. Bainbridge and Dale<sup>33</sup>, Kalk and Schöndube<sup>44</sup>, Kaznelson and Reimann<sup>23</sup>, Grebe<sup>54</sup> and Schöndube and Lürmann<sup>14</sup> have shown the relaxing effect of atropine on the gall-bladder due to its action on the vagus: therefore it seems inadvisable to give such substances as atropine in biliary drainage, these, as said before, tending to defeat the ends of the later administration of the cholekinetic agent. One found sodium bicarbonate, a substance without the disadvantages of atropine but with a similar relaxing effect on the pyloric sphincter, of definite help in assisting the passage of the tube into the duodenum (this was used of course only when difficulty was encountered). One noted that when no free hydrochloric acid was present in the fasting stomach contents it was rare to experience difficulty in reaching the duodenum: this was the experience also of Venables and Knott<sup>55</sup>. For many years it has been held that hydrochloric acid has, to some extent at least, a controlling influence on the closing of the pylorus. It is not necessary to empty the stomach of its contents as advocated by numerous investigators: after the patient has been turned on the right side the gastric contents begin to flow out of their own accord, it being necessary

however in an odd case to institute the flow by the withdrawal by means of a syringe of a few ccs.

After the tube has reached the duodenum, bile begins to flow: one does not find it necessary to have the patients screened to verify the position of the tube as one sees a continuous flow of light coloured bile (at times clear, at times somewhat muddy) which is alkaline in reaction as tested by litmus paper. Venables and Knott<sup>55</sup> also hold it is unnecessary to have the patients X-rayed to prove the tube is in the duodenum: they rely on a neutral or alkaline reaction to litmus paper for proof. Kalk<sup>39</sup> regards the appearance of clear light bile, which does not provoke a change in colour of Congo-paper, as sufficient proof of the duodenum having been reached. When one is satisfied the tube is in the duodenum and bile has been allowed to flow for some time to confirm this, being collected in test-tubes at intervals of 5 minutes, 2 cc. pituitrin are injected intramuscularly: incidentally the withdrawal of bile by means of a syringe is not necessary as bile flows from the tube of its own accord. (In one or two cases however it is necessary, at times, to use a syringe to clear the mouth of the tube which has apparently become blocked: after this has been done the spontaneous flow occurs again). The amount of pituitrin injected, although approximately twice the maximum dose advised, has never been observed to give rise to any untoward symptoms, at the most, in one or two cases, a call to stool and in a few others a little intestinal colic being complained of: Kalk<sup>3</sup> holds it is not often possible to obtain any response on the part of the gall-bladder with the usual doses of pituitrin i.e.  $\frac{1}{2}$  - 1 cc. The bile is again collected after pituitrin injection in test-tubes at 5 minute intervals: if after 1 hour no dark bile or bile which is only slightly dark in colour is obtained, 20 cc. of warmed olive oil are injected through the

tube into the duodenum, and the bile again collected in test-tubes at intervals of 5 minutes for another hour. At the end of this period the test is stopped unless dark bile is flowing at this time. This is a slight modification of Kalk's procedure; he, if having obtained no dark bile after 30 minutes, introduces oil and stops the test 10 - 20 minutes after this has been administered. He holds that pituitary extracts cause a response on the part of the gall-bladder in normal cases after 20 - 30 minutes and oil, after 10 minutes. In these investigations it was thought advisable however to wait for 1 hour after pituitrin had been injected, and for 1 hour after the administration of oil, to allow for a possible late response of the organ: as it happened this was justified in some of the cases. Incidentally the patients were able themselves to move the duodenal-tube every 5 minutes into the test-tubes used for the collection of bile, and therefore the constant attention of the writer was not necessary.

Bilirubin is estimated, as mentioned before, by means of the colorimeter in 2 specimens of bile, i.e. the lightest bile obtained before the injection of pituitrin and that which appears to the naked eye darkest after pituitrin and oil. In addition the sediment from the darkest specimens of bile, obtained after the use of pituitrin and oil, is examined microscopically.

#### NORMAL CASES.

It was decided to investigate by means of duodenal catheterization using pituitrin and oil normal cases in order to study the effect of these substances in such cases. One is faced, of course, immediately with the obvious difficulty of deciding whether in any given case one can be certain that the gall-bladder is normal, i.e. free from

disease: even presuming that no history suggesting in any way affection of the organ is obtained and that clinically no evidences of this are discovered on examination, one cannot say with certainty that the gall-bladder in such cases is normal. Burton<sup>56</sup> found in 5 out of 100 consecutive autopsies evidences of cholecystitis, although at no time had the patients complained of anything referable to the gall-bladder nor was anything noted clinically which pointed to such a condition. However where there is no possibility of one's opinion regarding the normal state of the gall-bladder being confirmed or disproved by operation or autopsy (preferably by histological examination), one is compelled to accept as normal cases, i.e. so far as the gall-bladder is concerned those without a history or clinical findings pointing in any way to disease of the organ. In these investigations 25 cases which conformed to this standard were examined by means of the duodenal tube. (One was able however in 5 of these cases to confirm, so far as is possible by operation and therefore macroscopic evidence, the fact that the gall-bladder was normal).

Certain conditions must of necessity be fulfilled before one can, using duodenal intubation and cholekinetic substances, obtain bile from the gall-bladder. These are 1). the gall-bladder must be present; 2). it must contain bile; 3). the cystic duct must be patent and 4). the gall-bladder must be capable of contracting sufficiently to expel the contained bile: to obtain a dark bile from the organ a fifth condition must be satisfied, i.e. the gall-bladder must possess the faculty of concentrating the bile which it has received from the liver. Obviously if the viscus does not contain bile because of recent previous contraction it is impossible to obtain any bile-outflow from it: the cystic duct may be blocked by stone (or



stones), by adhesions to neighbouring parts, kinking or conceivably by spasm of its sphincter: when any of these conditions are present no bile can be obtained from the bladder. Contractile power may be interfered with by fibrotic conditions of the wall, adhesions, etc. The power of concentrating, a very important function of the gall-bladder, may be affected by disturbance of the mucous membrane following inflammation: in addition, as regards the obtaining of dark bile from the organ, it is obviously necessary that the bile be in the bladder sufficiently long to allow of its being concentrated. It is clear that the presence of any one (or more) of these latter abnormal conditions would prohibit the obtaining of bile or of dark bile from the gall-bladder.

It might be well to give here the details of biliary drainage (pituitrin being used) in a typical normal case, case 20 being selected.

F. 18 years: convalescent after acute nephritis.

<u>No. of test-tube.</u>	<u>Mins.</u>	<u>Amount</u>	<u>Bilirubin mg. %</u>	<u>Colour</u>
1.	5.	1½ cc.	6	light lemon.
2.	10.	¾ cc.	4	" "
3.	15.	1½ cc.	8	" "
4.	20.	2 cc.	8	" "
5.	25.	5 cc.	20	light gold
6.	30.	4½ cc.	20	" "

Pituitrin (2 cc.) injected.

7.	5.	3½ cc.	20	" "
8.	10.	3½ cc.	40	dark gold
9.	15.	8 cc.	119	dark brown
10.	20.	7¼ cc.	132	" "
11.	25.	5 cc.	100	" "
12.	30.	1¼ cc.	96	" "
13.	35.	2½ cc.	104	" "
14.	40.	3 cc.	80	lighter brown
15.	45.	3½ cc.	80	" "
16.	50.	5 cc.	40	dark gold
17.	55.	2 cc.	40	" "
18.	60.	3 cc.	30	gold
19.	65.	2½ cc.	20	lighter gold
20.	70.	3 cc.	16	dark lemon

It will be seen from this case that shortly after pituitrin was injected, a flow of dark bile began of which the maximum bilirubin content was in the fourth specimen - 132 mg. %: towards the end of the test the bile became gradually lighter.

The results obtained in the 25 normal cases, using

pituitrin and oil, are set down in Table 1.

Age	Sex	Disease	Lightest bilirubin value (mg. %) before pit.	Highest bilirubin value (mg. %) after pit.	Highest bilirubin value (mg. %) after oil.
1.	32	M. Rheumatism	-	-	No oil given
2.	24	F. Hysterical vomiting.	-	-	" "
3.	39	F. Rheumatoid arthritis.	-	-	" "
4.	24	M. " "	-	-	" "
5.	20	M. Chronic nephritis.	2	280	" "
6.	32	F. Carcinoma (pancreas)	23	170	" "
7.	49	M. Appendicitis (recurrent)	6	6	174
8.	18	M. Pneumonia (recovered)	16	231	No oil given
9.	24	F. Chorea	12	90	110
10.	18	F. Pneumonia (recovered)	17	105	No oil given
11.	17	F. Bronchitis (recovered)	10	30	6
12.	32	M. Post-encephalitis	21	240	No oil given
13.	18	F. Pyelitis (recovered)	30	48	260
14.	51	M. Neurasthenia	10	160	No oil given
15.	28	M. Sub-acute nephritis	18	136	130
16.	26	F. Chorea	6	60	110
17.	53	M. Lateral sclerosis	25	240	20
18.	33	M. Chronic nephritis	7	25	16
19.	32	F. Appendicitis (recurrent)	5	60	84
20.	18	M. Acute nephritis (well)	4	132	20
21.	46	F. Migraine	8	8	220
22.	23	M. Disseminated sclerosis	10	75	16
23.	24	M. Anterior poliomyelitis (old)	4	240	No oil given
24.	45	F. Bronchitis	5	120	" "
25.	55	F. Appendicitis (recurrent)	8	68	83

(The diagnosis in cases 6, 7, 19 and 25 was made at operation: case 21 was also operated on).

It was noted that in cases 10 and 12 dark bile was not obtained until 45 and 40 minutes respectively after the injection of pituitrin, and in case 21 50 minutes after the administration of oil: this shows it is advisable to allow drainage to continue longer than Kalk advises.

One sees firstly, on examination of the above table, that the bilirubin-content of the bile obtained before the injection of pituitrin i.e. liver bile, varies between 2 mg. % and 30 mg. %. Kalk and Schöndube<sup>57</sup> are of the opinion that a bilirubin value in this bile of only 2 mg. % is too low, due to dilution of the bile by the gastric or pancreatic juices: Crohn, Reiss and Radin<sup>4</sup> believe also that when this bile is very light in colour dilution is probably the causative factor. Kalk<sup>39</sup> regards the average bilirubin content of liver bile as 14 mg. %, mentioning that the values may vary between 5 and 30 mg. %. In the cases in this series where this was estimated it was found that the average was approximately 12 mg. %, a figure which corresponds fairly closely with Kalk's: this average - as is Kalk's - is definitely higher than those accepted by Lepehne (referred to by Kalk and Schöndube<sup>57</sup>) and Deloch (quoted by Kalk<sup>3</sup>): they found the average bilirubin content of liver-bile to be between 1.5 and 4.5 mg. % and 1 and 5 mg. % respectively.

Kalk and Schöndube<sup>57</sup> hold that on the average the bile expelled from the normal gall-bladder contains 18 times the amount of bilirubin that liver bile does: this is an appreciably higher figure than that accepted by Ignatowski and Monossohn and Hammersten (~~both~~ quoted by Kalk and Schöndube) who regard the average as 7 - 8 times and 10 times respectively. In a review<sup>58</sup> of Chiray and Thiebaut's newest book on hepatic and biliary-tract function, exception is taken to the authors'

opinion that the gall-bladder concentrates liver-bile only 4 - 5 times, i.e. the pigment value of gall-bladder bile is only 4 - 5 times that of liver bile, the reviewer mentioning that Rous has shown that this is too low and that a concentration power of 10 times is possessed by the organ. In these investigations one finds a concentrating power of the gall-bladder varying from 7 to 23 times (excluding those cases where the bilirubin content of the liver bile was below 5 mg.%), but one doubts if it serves any useful purpose attempting to strike an average as regards this particular faculty of the organ.

Kalk<sup>3</sup> and Schöndube<sup>12</sup> have noted that in some cases the gall-bladder ~~was~~ <sup>is</sup> able to produce bile that had <sup>s</sup> 90 times the pigment content of the liver bile. One feels it would be better to say simply that it is within the power of the normal organ to concentrate the bile it receives from the liver to varying degrees of which the greatest is 90 times (as shown by Kalk and Schöndube): in one word the power of bile pigment concentration possessed by the normal gall-bladder may be comparatively slight or very marked.

Naturally to arrive at a decision by means of biliary drainage as to when the gall-bladder is functioning fully as regards its concentrating power (and therefore probably as regards its other functions also) is no easy matter. Kalk<sup>3</sup> & 39, Kalk and Schöndube<sup>57</sup> insist on the obtaining, after the use of pituitary extracts, of bile with a bilirubin content of at least 100 mg.% before one is entitled to speak of what they call a positive result, i.e. one indicating that the gall-bladder has a normal concentrating ability and is there probably free of disease (Kalk and Schöndube accept however in one of their cases 90 mg.% as a normal result). This standard is an arbitrary one, and as with all arbitrary standards a certain amount of care must be exercised when applying it.

In this series of normal cases as set down in Table 1., it will be observed that no figures for the bilirubin content of the bile, obtained by duodenal catheterization before and after pituitary injection, stand opposite the first 4: these were investigated before the colorimeter was obtained, but from the colour of the gall-bladder bile one was able, having had some experience of the colorimetric estimation of bilirubin previously in Berlin, to decide fairly accurately that the bile had a bilirubin content of well over 100 mg.%. In the 25 normal cases here investigated 16 satisfied the standard set by Kalk and Schöndube, i.e. bile having a bilirubin value of 90 - 100 mg.% and over was obtained from the gall-bladder by the use of pituitrin. This is not in agreement with the findings of Kalk and Schöndube<sup>57</sup> who in 24 normal cases found that all of these gave what they term a positive result. 9 of the 25 normal cases did not satisfy Kalk and Schöndube's standard. This point was raised verbally with Kalk recently, and he expressed the view that such cases should not be regarded as cases with normal gall-bladders but as examples of "dyskinesie", i.e. cases of functional disturbance of the extrahepatic biliary system in patients with "upset" of the hormonal and vegetative nervous systems. He recognises 3 types of "dyskinesie" - hypotonic, hyperkinetic and hypertonic - but the existence of such an entity as "dyskinesie" is merely a presumption to explain findings which are unusual, and one feels one is not entitled, until the subject is investigated further and the existence of the condition proved conclusively, to regard cases where the gall-bladder does not react to pituitary extracts, in what Kalk holds to be a normal manner as examples of functional disorder of the organ (one refers, in this connection, only to cases where no history is given nor clinical findings suggesting gall-bladder disease are discovered). Incidentally Lyon<sup>2</sup> questions the existence

of purely functional disease of the gall-bladder. One explanation of the negative result to pituitrin in these 9 cases might be regarded as specious, i.e. poor quality of the pituitrin used. Trendelenburg<sup>59</sup> pointed out that pituitary extracts are often unreliable in action and should be of a definite titre to ensure reliability: Jones<sup>60</sup> drew attention to this matter also. The pituitrin however which was used in these investigations was all of the same manufacture and often indeed from the same stock: it is recognised as reliable and produced a positive result in 16 cases. Therefore one may presume the pituitrin was not at fault.

In 23 of Kalk and Schöndube's<sup>57</sup> normal cases the bilirubin content of the bile obtained from the gall-bladder by the use of pituitary extract was estimated with the following results - 1 was under 100 mg.%, 7 were between 101 and 200 mg.%, 7 between 201 and 300 mg.%, 6 between 301 and 400 mg.%, 1 between 401 and 500 mg.% and 1 over 600 mg.%. In the 12 normal cases investigated by the writer in which a positive result was obtained after pituitrin and the bilirubin content of the gall-bladder bile estimated, the findings were as follows:- under 100 mg.% 1, between 101 and 200 mg.% 6, between 201 and 300 mg.% 5. It is certainly striking that the highest bilirubin value of gall-bladder bile in these cases was 280 mg.% whereas Kalk and Schöndube found in their 23 cases that 8 had values above 300 mg.%. Schöndube<sup>12</sup> mentions that the pigment content of the bile obtained from the gall-bladder after pituitary extracts is usually over 200 mg.%, and Campanacci and Groppali<sup>61</sup> using ergotamin found the bilirubin content of this bile to be 360 mg.% (this latter is, however, the result of only 1 case). In 2 cases with pathological

gall-bladders (to be mentioned later) the gall-bladder bile showed bilirubin values of 313 mg.% and 442 mg.%. On the whole the values of the gall-bladder bile as regards bilirubin content found in these pituitrin-positive cases were appreciably lower than those obtained by Kalk and Schöndube in normal cases: no significance attaches probably to this, and it is almost certainly to be explained by <sup>the</sup> fact that, as shown before, the concentration-power of the gall-bladder varies markedly in different individuals.

In 4 of the normal cases investigated which did not give what Kalk terms a positive result after the injection of pituitrin, such a result was obtained with oil. In 2 of them (13 and 16) some response was observed after pituitrin, but oil was necessary to call forth a flow of bile having a bilirubin content of over 90 - 100 mg.%; in the other 2 (7 and 21) the gall-bladder did not respond by contraction to pituitrin. As mentioned before Kalk<sup>3</sup> insists that to presume a gall-bladder is normal a positive result must be produced by the use of pituitary extracts. He found oil an extraordinarily good cholekinetic substance but insists that pituitary extracts are more reliable in their action on the gall-bladder and allow of a more subtle diagnosis of disease of the organ being made: he goes so far as to say that cases which do not give a positive result with pituitary extracts but do so with oil are not normal, a degree of gall-bladder disease being present. But in 2 of the 5 cases operated on in which the gall-bladder was found normal at operation, pituitrin caused no appearance of bile from the gall-bladder, whereas oil allowed of a positive result being obtained. One is compelled to



take the view that in 2 of these 4 normal cases oil provided a stimulus to the gall-bladder where pituitrin failed to do so, and in the other 2 it provided a stronger stimulus to the organ than pituitrin.

5 normal cases in this series failed to give a positive result with either pituitrin or oil: one accepts here for the moment the view expressed by Kalk and Schöndube (ignoring the emphasis laid by them on the results obtained with pituitary extracts) that to presume a gall-bladder is normal it is necessary to obtain from the organ, by the use of cholekinetic agents, bile with a bilirubin content of over 90 - 100 mg.%. In 3 of these bilirubin values, i.e. of gall-bladder bile, of 60 mg.%, 68 and 75 mg.% respectively were obtained after pituitrin and in 2 of them a response to oil was also obtained (84 mg.% and 83 mg.%). The results in these 3 cases bring one back at once to the question of the normal standard set by Kalk and Schöndube regarding the concentrating power of the gall-bladder. The point immediately arises - is it possible for a gall-bladder, normal in every way, to concentrate bile which has a bilirubin content of only 60 mg.%? Kalk has admittedly extensive experience of biliary drainage in pathological cases, but still his standard impresses one as being somewhat arbitrary: arbitrary standards are necessary in medicine, but most standards in bio-chemical medicine allow - must allow - of a fair range as regards the normal value. One admits that the usual bilirubin content of normal gall-bladder bile is above 90 - 100 mg.%, but one may well suppose that there are normal cases which give somewhat lower values. Kalk and Schöndube<sup>57</sup> obtained in all of their 24 normal cases bilirubin values of gall-bladder bile of 90 mg.% and over; in these investigations

there were 23 cases which showed some response although varying to pituitrin and/or oil: the number of cases in both series is small and one questions the advisability, from the results of so few cases, of setting - or attempting to set - a standard which is of necessity somewhat arbitrary and therefore not quite reliable. One is compelled from the investigations of these presumably normal cases to take the view that there are normal individuals, admittedly in the minority, whose gall-bladders concentrate bile which shows a pigment-value of less than 90 mg.%, the standard set by Kalk and Schöndube.

2 cases failed to respond by gall-bladder contraction to either pituitrin or oil, and one finds oneself again running counter to the views held by Kalk and Schöndube. Such a finding allows of little or no discussion - the fact stands out. One could, as a means of explaining the absence of any response on the part of the gall-bladder in these cases, make use of Kalk's and Westphal's (referred to by Kalk<sup>3</sup>) theories regarding "dyskinesie", but for the purpose of these investigations, for reasons already mentioned, these must be ignored. So must other causes of absence of response to pituitrin and oil, for it has been stated early on that the cases in this part of the series are regarded for the purpose of assessing the value of these 2 substances in biliary drainage as normal cases. The only explanation of the lack of gall-bladder response can be that neither pituitrin nor oil was able in these 2 cases to produce contraction of the organ and expulsion of its contents. Such possibility is borne out by the observations of Crohn, Reiss and Radin<sup>4</sup>: they noted that in some cases the gall-bladder could not be induced to

expel its contents by the use of various substances which frequently caused this, although at operation nothing was discovered to account for this failure of response. The opinions of Held and Goldbloom<sup>8</sup> in this connection are also to be remembered: while they do not deny that pituitrin can cause the gall-bladder to contract and empty they did not find it so reliable in its action as Kalk. Adlersberg (referred to by Held and Goldbloom<sup>8</sup>) holds that pituitrin exercises its cholekinetic effect through the central nervous system, particularly the base of the brain: he suggests that in those normal cases, where the drug fails to produce contraction of the gall-bladder, there is possibly a temporary functional disturbance of this part of the brain. This explanation is certainly specious but too fanciful to be convincing. Pribram,<sup>17</sup> while working with magnesium sulphate, observed that in some cases without any evidences of gall-bladder disease it was impossible to obtain by duodenal catheterization bile from the gall-bladder in spite of all efforts and repeated attempts. One may therefore with justification assert that there are cases with normal gall-bladders where the organ cannot be caused to contract by pituitrin and oil, just as there are some that do not respond to peptone, magnesium sulphate etc.

3 cases amongst those investigated in this series of normal cases are worthy of further mention:- Case 6:- a tumour was palpable in the region of the gall-bladder, although a little lower and more medial than the usual situation of this organ: this was diagnosed by the surgeon as probable neoplasm of the gall-bladder. Duodenal catheterization showed,  $7\frac{1}{2}$  minutes after the injection of 2 cc. pituitrin, a flow of dark bile, the highest value of bilirubin in this being 170 mg.%. At operation carcinoma of the head of the pancreas was found while the gall-bladder and ducts were normal.

Case 7:- patient complained of periodic attacks of pain in the right hypochondrium during the previous year: he vomited during the attacks and fatty foods "upset" him as a rule: the pain during some of the attacks was felt also in the region of the angle of the right scapula. Cholecystography showed no filling of the gall-bladder. Duodenal intubation showed no response to pituitrin but dark bile, of which the highest bilirubin value was 174 mg.%, was obtained after oil. Operation revealed a normal gall-bladder but an appendix which showed signs of recurrent inflammation: the appendix was long, ascending behind the ascending colon but lying clear of the gall-bladder.

Case 21:- patient complained of periodic attacks of bilious vomiting with associated headache: cholecystography showed no filling of the gall-bladder. The case was diagnosed by the writer as probable migraine, but the surgeon and another physician suspected gall-bladder disease. Biliary drainage showed a positive result after oil (no response being obtained with pituitrin), bile having a biliary<sup>rubin</sup> content of 220 mg.% being obtained. Operation revealed a perfectly normal gall-bladder.

It will be seen from these 3 cases that the results of biliary drainage, using pituitrin and oil, suggested that the gall-bladder was functioning well and<sup>was</sup> therefore probably normal: this was confirmed by operation. In 2 of them X-raying, after Tetraiodphenolphthalein had been given, showed no filling of the gall-bladder, leading one to suspect a gall-bladder lesion.

PATHOLOGICAL CASES.

33 cases of gall-bladder disease were investigated by means of duodenal catheterization using pituitrin and oil. Cases with marked jaundice clinically attributable to gall-stones were not investigated nor was the test carried out if possible until all acute symptoms had gone. Of these 33 cases 23 came to operation so that one was able in these cases at least to verify the results obtained. One proposes to mention first these operated cases.

In only 2 of these cases was bile of a bilirubin content of over 90 - 100 mg.% obtained from the gall-bladder, in 1 case after the use of pituitrin and in 1 after the use of oil: in some of the others some response was observed after the use of these cholekinetic agents. One seeks now for a possible reason for the results obtained, bearing in mind the chief aforementioned conditions necessary for the obtaining of a dark bile from the gall-bladder: these are in short, 1). patency of the cystic duct, 2). adequate contractile, and 3). adequate concentrating power of the organ.

In 8 of the cases the cystic duct was found at operation completely obstructed by stone so that even if changes in the wall had not been present and the organ had therefore preserved its full power of contracting and concentrating, it would have been impossible for bile to escape from the gall-bladder. As would be expected from such operation findings no dark bile was obtained by duodenal intubation after the use of pituitrin and oil. In another case where stones were found in the cystic duct a response on the part of the gall-bladder was observed after the use of olive oil: this was remarkable

in so far as the flow of dark bile lasted only 5 minutes, a most unusual experience: the bilirubin value of this bile was 68 mg.%. At operation a gall-bladder with thickened wall, which was adherent to surrounding structures was found: in addition 2 stones were found in the cystic duct, but these were moveable. One presumes that these stones were, during most of the test, obstructing the cystic duct, but that during the short period when dark bile was obtained they dislodged themselves sufficiently to allow of the passage of bile from the bladder. The wall, in spite of being somewhat diseased, was still capable of contracting and concentrating bile to some degree.

Kalk<sup>3</sup> investigated in all 200 pathological cases and of these 44 came to operation: of these 44, 26 gave what he terms a negative response to pituitary extracts, i.e. bile having a bilirubin value of less than 90 - 100 mg.% was obtained ~~from the gall-bladder~~ and in 10 of these 26 cases he discovered at operation complete obstruction of the neck of the gall-bladder or of the cystic duct by stones: in another case the obstruction of the cystic duct was due to inflammatory adhesions. One sees therefore that in this series of pathological cases the frequency of obstruction of the cystic duct and consequent absence of response to pituitrin and oil corresponds fairly closely with that noted by Kalk in his cases.

Kalk<sup>3</sup> found in 9 of his 26 operated cases which gave a negative response to pituitary extracts changes in the gall-bladder which he held rendered it incapable of adequate contraction <sup>or</sup> ~~and~~ concentration; <sup>or both</sup> these were of the nature of inflammatory changes in the wall, i.e. breaking down of musculature with its replacement by fibrous tissue and affection of the mucous membrane: in 4 of his cases

the gall-bladders showed evidences of acute inflammation. In another 6 (1 will be referred to more fully later) of the 23 cases here referred to no response was observed after the use of pituitrin and oil: in these cases obvious signs of disease of the wall of the organ were discovered at operation. One is entitled from this to presume that in these cases the gall-bladder had been so altered by inflammatory changes that it had lost its power of concentrating or contracting, <sup>or both. 5</sup> In  $\frac{1}{2}$  cases ( $\frac{1}{2}$  will be referred to more fully later) dark bile was obtained from the gall-bladder after the use of pituitrin, the bilirubin value varying from 50 to 74 mg.%. This does not reach the standard set by Kalk and Schöndube for normal concentrating power of the gall-bladder and would be regarded by them as affording proof that the organ was in these cases diseased. One did note however, in a few of the normal cases investigated in this series, that the contents of the gall-bladder did not show the bilirubin value demanded by Kalk and Schöndube as proof of normal organs. In 4 of these latter cases a definite reason could be found to account for the gall-bladder bile's not possessing at least the bilirubin content regarded by Kalk and Schöndube as the lower limit of the normal, i.e. 90 - 100 mg.%. the wall of the organ was affected by inflammatory changes in these cases. The gall-bladder in these cases had apparently retained its power of contracting but, if one accepts Kalk and Schöndube's standard, the concentration-power had suffered somewhat. One thing however remains clear, i.e. that diseased gall-bladders can on occasion contract and expel bile showing such a pigment-concentration as is to be seen at times in the normal organ. One might in this connection make reference to 2 cases which showed - 1 after pituitrin and 1 after oil - dark gall-bladder bile with a high

bilirubin content: the bile in these cases had pigment values of 136 mg.% and 138 mg.% respectively. At operation stones were found in the organ in both cases: histological examination of both gall-bladders was made by the pathologist, and the following reports were furnished:-

- a) "gall-bladder wall shows evidences of slight cholecystitis with submucous fibrosis: mucous membrane somewhat atrophied and catarrhal."
- b) "gall-bladder wall presents a relatively normal appearance."

The obvious conclusion is that the organ in these two cases, in spite of the presence of stones, and inflammatory changes in at least one of them, had preserved not only its power of contraction but also the ability to concentrate bile to a marked degree. It is interesting to note that in one of these cases the history and clinical findings were not particularly suggestive of a gall-bladder lesion, the pre-operative diagnosis being made by chance during radiological examination for another condition. Although cholecystitis is usually associated with cholelithiasis, one finds at times at operation stones without there being any marked or any change in the wall of the organ. Kalk<sup>3</sup> observed that cases of cholelithiasis may give a positive response to pituitary extracts: this he noted in 17 out of his 200 cases investigated.

One case - 21 - deserves special mention: in this case no dark bile was obtained after the use of pituitrin and oil, but at operation an apparently normal gall-bladder was discovered. The bile in the organ was very dark, and on estimation of its bilirubin content a high figure, i.e. 442 mg.%, was obtained. One sought for the possible cause of the bladder's not being able to expel its bile, and a piece of the wall was excised and examined microscopically: signs of chronic and subacute cholecystitis were observed



and in addition a pure growth of streptococci was obtained from the wall. This is obviously a case where the gall-bladder was diseased, but only its contractile power was affected, the concentration power being still maintained. Kalk<sup>3</sup> holds that gall-bladder bile having a bilirubin value of over 400 mg.% is usually indicative of abnormal concentration on the part of organ and suggests stasis: undoubtedly st~~asis~~ is suggestive of defective motor action on the part of the viscus.

In 2 of the operated pathological cases no gall-bladder was found at operation: in 1 case the organ had sloughed off and in the other had been removed some years before, although this was not definitely known before operation. The cause in these cases of the absence of any response to pituitrin and oil is obvious and needs no explaining. It is interesting to note that in the case where the gall-bladder had been removed the liver bile was not darker than normal: Kalk<sup>3</sup>, Judd<sup>7</sup>, etc., as mentioned before, hold that the ducts may take on compensatory powers of bile concentration after the removal of the gall-bladder.

From these pathological cases which came to operation one sees that the commonest cause of inability to obtain any bile from the gall-bladder after the use of cholekinetic agents is obstruction of the cystic duct by stone: this is in accord with Kalk's findings. After this comes inflammatory damage to the wall of the gall-bladder. In addition gall-bladders, even if diseased, may maintain their power of contracting and of concentrating bile to various degrees.

UNOPERATED PATHOLOGICAL CASES.

10 cases of clinical gall-bladder disease were investigated but did not come to operation: therefore it was impossible to confirm the diagnosis suggested by means of biliary drainage (with history and clinical findings). Of these 5 showed absolutely no response by the outflow of dark bile from the gall-bladder to pituitrin and oil while 4 showed some response to pituitrin (very dark bile being obtained in 1 of these after oil): 1 showed some response to oil only. The highest bilirubin value in 4 of these cases was 51 mg.%, but in 1 case which responded only slightly to pituitrin, the bilirubin content of the bile obtained after oil was 313 mg.%. Therefore in 9 of these 10 cases the clinical diagnosis was supported by duodenal catheterization, i.e., if one accepts the standard set by Kalk and Schondube: it is easier in these cases to accept it as the values of bilirubin in the gall-bladder bile obtained were comparatively low, the highest being 51 mg.%. The case which gave a positive response to oil is interesting: the test was done more than 10 days after the acute pain had subsided, and the result supports Kalk's<sup>3</sup> contention to which reference has already been made. He holds that, in recovery from acute inflammatory disease of the gall-bladder, the pituitrin test may be negative while a positive response is given to oil: later both tests may give positive results. This he explains by assuming that pituitary extracts allow of a more subtle diagnosis being made: if his contention were right - it is not being accepted in these investigations - one would explain the result in this case by taking the view that the inflammation had so far recovered as to permit of the organ's contracting normally to oil but not to pituitrin: unfortunately the patient did not remain long enough in hospital to allow of a 2nd intubation to discover if, after complete recovery, pituitrin would have been able to produce

expulsion from the gall-bladder of the fully concentrated contents.

One case in this series had had 2 attacks of typhoid fever and blood examination showed a slightly positive Widal reaction: it was decided to have the bile examined for typhoid bacilli, it being well known that in such an individual they are often to be found in the gall-bladder. Nothing was discovered bacteriologically which however was not surprising so far as the gall-bladder was concerned, for no bile was obtained from the organ after the use of pituitrin and oil.

The cause of the absence of response or poor response to pituitrin and oil in these cases is, as no operation was undertaken, a matter of conjecture. 5 cases showed no response to these substances, and in these cases the cystic duct may have been obstructed or the gall-bladder wall may have been so changed by inflammation that the organ was not able to contract or concentrate the bile <sup>(or both)</sup> ~~it~~ received from the liver; <sup>(or both)</sup> from the results obtained in the operated cases one may presume that obstruction of the cystic duct was the probable cause in the majority of these cases. In 1 of these 5 cases the cystic duct was patent at least when cholecystography was done, for a faintly filled gall-bladder was seen radiologically after the administration of Tetraiodphenolphthalein. In the other 4 where only a poor response was observed after pituitrin or oil, one may presume that inflammatory changes in the wall of the organ were responsible for the absence of marked concentration of the bile. In one of these cases only a very small amount of dark bile was obtained, the flow occupying at the most 5 minutes: this finding is similar to that obtained in the operated cases, to which reference has been made, where moveable stones were found in the cystic duct. Possibly the explanation in this case is that suggested for the latter. In short, the causes

giving rise to the findings in 9 of the 10 cases investigated here were probably similar to those producing like results in the operated cases.

It was observed that in some of the pathological cases the bile obtained by means of the tube was of an olive colour or was very viscous : the number of cases where this was seen was comparatively small and therefore it is very difficult to say whether the finding of such bile is significant of disease of the biliary tract or not. In addition, in 2 cases some little time after pituitrin had been injected some discomfort was complained of in the region of the gall-bladder: this leads one to presume that in these cases pituitrin caused contraction of the organ which, because of the presence of stones or inflammation, made itself noticeable to the patient. Kalk<sup>3</sup> lays particular stress on such an occurrence, holding it is strongly suggestive of a gall-bladder lesion.

The results in this series of pathological cases are different from those obtained by Kalk<sup>3</sup>: he investigated however 200 cases while here only a small number was examined by duodenal catheterization: one must bear this in mind when comparing the results. Kalk found that in his 200 cases - judged according to the standard set by him and Schondube - 66 gave a positive result, 103 a negative result and the remaining cases a result which was at one time positive, at another negative (as, in these investigations, the test was done only once in each patient, no cases <sup>5</sup> showing such a result could be observed). The discrepancy is marked: Kalk, using of course only pituitary extracts, obtained in  $\frac{1}{3}$  of his pathological cases bile from the gall-bladder which had a bilirubin content of 90 - 100 mg.% and over, while in this series only 3 out of a total of 33 cases gave such a result

(2 only after oil, which Kalk holds is abnormal): therefore in  $\frac{1}{3}$  of Kalk's cases biliary drainage gave, according to him, a fallacious result whereas in this series only 1 out of 33 gave what he would term a fallacious result. From these latter results one could assert that biliary drainage employing pituitrin and oil is an excellent means of testing the function of the gall-bladder and therefore of assisting in the diagnosis of disease of the organ, if one accepts the standard set by Kalk and Schondube: one is however not prepared to accept this absolutely. It must be remembered that there are normal gall-bladders, admittedly in the minority, which do not concentrate bile received from the liver to the degree set by Kalk and Schondube as normal: in addition, a very small minority of normal gall-bladders do not respond at all by the expulsion of their contents to pituitrin and olive oil. On the other hand, a percentage of cases with definitely diseased gall-bladders may expel bile with bilirubin values corresponding fairly closely with those obtained on occasion in normal cases while at times, admittedly seldom, ~~gall-bladder~~ bile of a concentration satisfying Kalk and Schondube's standard may be obtained from gall-bladders which are diseased. The question arises - when can one by the use of pituitrin and oil in biliary drainage make a diagnosis of functional disturbance of the gall-bladder due to disease? From the results of the foregoing cases one would be entitled to say that when after the injection of pituitrin (or in some, after oil) a dark bile having a bilirubin content of over 90 - 100 mg.% is obtained the gall-bladder is probably normal: this agrees more or less with Kalk's views without being of course absolute: conversely when no bile is obtained from the organ after the use of these cholekinetic agents one may make a diagnosis of gall-bladder disease: this too is not absolute. When some response on the part of the gall-bladder is observed

after pituitrin and ~~for~~ oil and the bilirubin value of the gall-bladder bile is less than 90 - 100 mg.% the establishing of a diagnosis is more difficult. One would be inclined to suggest that when no history nor clinical findings suggesting a lesion of the gall-bladder are obtained and when a response on the part of the organ to pituitrin and oil is absent or the gall-bladder bile does not reach the standard as regards bilirubin content set by Kalk and Schondube, one should be chary of diagnosing disease of the gall-bladder. On the other hand, when a history and ~~for~~ findings pointing to possible disease of the organ are obtained and no bile is expelled from the bladder or bile whose bilirubin value is under 90 - 100 mg.%, one can with a degree of assurance make the diagnosis of a pathological condition of the gall-bladder: in these latter cases biliary drainage is of course only a means of confirming the diagnosis made clinically, the latter certainly not standing or falling by the result of the test.

Little reference has been made to cholecystography in these investigations. It would have been a method of confirming or disproving the results, in the normal and pathological cases, of biliary drainage, but one's experience with the oral administration of such substances as Tetraiodphenolphthalein (the method most often used in this country) and subsequent X-raying has not been good: one has formed the opinion that only when a good shadow of the gall-bladder is to be seen, proving that the cystic duct is patent and that the organ is capable of concentrating well, is oral cholecystography of value: when no filling or only a faint shadow is seen, little can be deduced from this - in the latter case one knows however that the cystic duct is not obstructed. The intravenous method of administering the contrast substance is certainly much more

reliable than the oral method at present in use. Lately the writer has been employing a modified oral method advocated by Sandström,<sup>62</sup> and the results are certainly more reliable than those obtained by the ordinary oral method: in addition when egg yolk and cream are administered orally after the gall-bladder has been visualised, one is able to test the contractile power of the organ. This method shows promise, but the writer feels many more cases must be investigated before any opinion regarding its utility can be expressed. One must remark that the opinions expressed here regarding the oral method of cholecystography are the results of one's personal experience and are not in accord with those of all clinicians who employ this method.

#### SEDIMENT EXAMINATION.

In the pathological cases where one was sure that bile was obtained from the gall-bladder and in some of the normal cases, the sediment from this bile was examined microscopically in order to discover if any help could be obtained in deciding on the condition of the organ. Admittedly these cases were comparatively small in number only  $\frac{1}{10}$  of the 33 abnormal cases showing any response to pituitrin: in 2 cases oil alone produced an outflow of bile from the gall-bladder, but the sediment examination in these cases was rendered difficult by the presence of fat globules which occupied the fields almost completely, and it was practically impossible to see anything but these globules. One would expect that the examination of the gall-bladder bile in pathological conditions of the organ would show abnormal constituents which would assist in the arriving at a diagnosis of the presence of inflammatory changes in the wall and for stones.

The value of microscopic examination of the bile sediment in pathological conditions of the gall-bladder has provided for years ground for discussion, but the majority of investigators in this field regard it as being a valuable aid in the diagnosis of disease of this organ. Lyon<sup>2</sup>, Jones<sup>50</sup>, Knott<sup>63</sup>, Hurst<sup>47</sup>, Piersol, Brockus and Shay<sup>64</sup>, Kalk<sup>3 & 39</sup>, Hollander<sup>41</sup>, Hunt<sup>53</sup>, Dicks<sup>10</sup>, Shay, Tumen and Rodis<sup>65</sup> and Pennetti<sup>45</sup> all believe that microscopic examination of the bile obtained from the abnormal gall-bladder by duodenal catheterization is of great use in the diagnosis of the condition present in the organ. The sediment findings of these investigators vary somewhat, and each of them tends to stress the importance of the presence of different unusual constituents in the sediment. Piersol, Brockus and Shay for instance place great weight on the finding of calcium bilirubinate crystals, while Hunt holds these have little significance and are found in normal cases. On the whole however these investigators agree that the presence in the gall-bladder bile sediment of excess of leucocytes, excess of cholesterol crystals, gall-bladder epithelial cells and calcium bilirubinate masses ~~is~~<sup>is</sup> very suggestive - some hold even definitely diagnostic - of gall-bladder lesions; they are, so these investigators hold, indicative of inflammatory changes of the organ or of the presence of stones or both.

On the other hand Fitz and Aldrich<sup>66</sup>, Bassler, Lockett and Lutz<sup>5</sup> and Crohn, Reiss and Radin<sup>4</sup> take the view that the microscopic findings in the sediment obtained from gall-bladder bile in pathological cases are indefinite and not of any diagnostic value. Fitz and Aldrich found that the microscopic examination of bile from resected diseased gall-bladders gave inconsistent results and emphasize the fact that bile analysis in general, i.e., cholesterol content,



total nitrogen, urea nitrogen together with the examination of the sediment, is of little or no value in the diagnosis of gall-bladder disease. Bassler, Luckett and Lutz maintain that the margin of error in the deducing of disease of the organ from the presence in the bile of muco-purulent flakes, inflammatory debris and cells is too great for such examination to be of any clinical value. Crohn, Reiss and Radin were able to discover often <sup>1</sup>neucocytes and detritus in the bile obtained from the gall-bladder by biliary drainage but were unable to observe these when bile was taken from the organ during operation: in addition they noted at times that cholesterol crystals were present in increased quantities in the gall-bladder bile, and yet no stones were found in the organs at operation.

In the pathological cases in this series where bile was obtained from the gall-bladder after the use of pituitrin and the sediment examined microscopically, no help was obtained as regards diagnosing the condition of the organ. On the whole the findings were similar to those obtained in the normal cases. Cellular debris, calcium bilirubinate and other crystals with occasional epithelial cells were observed in the gall-bladder bile in both normal and pathological cases, and in none of the latter were the findings sufficiently definite to allow of a diagnosis of the condition of the organ being made. The most common finding in both types of cases was cellular debris and granular material, but it was found impossible to identify these: one felt that the cellular debris might have been in part composed of leucocytes, but this could not be asserted with confidence. Fitz and Aldrich were unable also to identify the cellular debris and granular material they saw in the sediment. Piersol, Bockus and Shay observed the presence of crystalline material as was noted in these investigations but consider it of no significance.

Lyon (referred to by Dicks<sup>10</sup>) and Kalk<sup>5</sup> admit that in pathological conditions of the gall-bladder one may find in the bile obtained from the organ by biliary drainage no abnormal constituents. Admittedly the gall-bladder bile, in the pathological cases so investigated in this series, was mixed with stomach and duodenal contents, a fact which rendered the microscopic examination somewhat difficult, but the aforementioned investigators, with the exception of Kalk, were faced with the same difficulty. The bile in these investigations was centrifuged with an ordinary electric centrifuge and not with a high-speed apparatus which Jones<sup>50</sup> insists is necessary for the obtaining of reliable sediment results: one presumes however that other investigators employed also an ordinary centrifuge.

One is not prepared to dogmatize as regards the utility or lack of utility of the microscopic examination of bile obtained from the diseased gall-bladder by means of duodenal catheterization, because so few cases were investigated by this method. All that one can say is that in these investigations no assistance was obtained in any case from such an examination, i.e. as regards the establishing of a diagnosis of the particular lesion of the gall-bladder.

#### LIVER INVOLVEMENT IN GALL-BLADDER DISEASE.

That the liver is somewhat affected in most cases, at least of long standing of gall-bladder disease, is a generally recognized fact. Graham<sup>27</sup> was able to show by microscopic examination of sections of the liver removed at operation that hepatitis is a constant accompaniment of cholecystitis. Jones<sup>50</sup> also found that this organ is often involved in inflammatory conditions of the gall-

bladder with or without the presence of stones. The frequent involvement of the liver in gall-bladder disease was observed also by Heyd, Killian and McNeal (referred to in B.M.J.1930): they noted in association with biliary tract disease a generalized hepatitis extending far beyond the neighbourhood of the gall-bladder. Flint<sup>67</sup> was able to confirm Graham's findings, observing hepatic involvement very commonly in disease of the gall-bladder. Walton's<sup>68</sup> findings in cholecystitis were similar. Rivers and Hartmann<sup>69</sup> however hold that liver involvement in disease of the gall-bladder is not so common as other investigators would have it: their figures were - 18.9% in cholecystitis and 12.7% in cholelithiasis: on the other hand, Mentzer,<sup>70</sup> investigating 548 cases which came to autopsy and studying sections removed from various parts of the liver, found the occurrence of hepatic involvement to be much more frequent - 60% in non-inflammatory disease of the gall-bladder and 97% in inflammatory disease. Cantarrow and Gehret<sup>71</sup> concluded from their investigations that all patients with biliary tract disease should be regarded as having hepatic damage, with or without functional disturbance of the organ. One may therefore assume that in cases of gall-bladder disease, at least of long standing and particularly where inflammation has taken place, the liver is somewhat affected.

Kalk<sup>3</sup> in almost all of his pathological cases determined the bilirubin content of the blood serum as a means of deciding if the liver was involved in these: He holds that in cases of cholecystitis with or without stones, the bilirubin value in the blood is regularly increased, especially in the period following the acute attacks of pain, and this he attributes to a degree of hepatic affection. He mentions however that the results obtained by this examination should be used diagnostically with extreme care. Flint<sup>67</sup> used, as a clinical method of deciding the presence of liver involvement in gall-bladder disease, the van den Bergh and laevulose

tests: with regard to the increase of bile-pigment in the blood as shown by means of the former he considers it to be due to interference with the polygonal cells, sometimes by poisoning and sometimes by damming back of the bile in the smaller ducts (microscopically he found some of these to be compressed) and at times by both.

The method used in these investigations of arriving at the bilirubin content of the blood-serum was that employed by Kalk<sup>3</sup>, i.e. van den Bergh's quantitative method using the Hellige colorimeter. In 19 of the pathological cases investigated the bile-pigment content of the blood was ~~examined~~ <sup>estimated</sup>. In the remainder of the abnormal cases this examination was not carried out because it was impossible to obtain blood without disturbing the patients unduly: most of the patients were females, and one knows that females with gall-bladder disease are often stout, a fact which renders vein puncture difficult and at times impossible. Kalk<sup>3</sup> sets .8 mg.% as the upper limit of bilirubin in the blood in normal cases but earlier, while working with Siebert<sup>72</sup>, he regarded .87 mg.% as the maximum found in such cases. Förster<sup>73</sup> regards, however, values as high as 1 mg.% as being within normal limits. In the cases in these investigations where this examination was employed only 2 showed blood bilirubin values above the upper limits set by Kalk and Siebert and Förster<sup>73</sup>, these being 1.6 mg.% and 2.25 mg.%: it is noteworthy that in these 2 cases a degree of jaundice was to be observed clinically, and it was therefore no surprise to find an increase of bile-pigment in the blood. In all the other pathological cases so investigated normal values, according to the standards of the above-mentioned investigators, were found.

The question now arises - if a normal bile pigment value in the blood is obtained is this definite proof that the liver is normal? Willcox<sup>74</sup> points out that such tests

as the van den Bergh and icterns index estimation are of value only in indicating the action of the bile regulating mechanism of the liver, and that this is not a liver function of vital importance. Rolleston<sup>75</sup> emphasizes that the tests for any one function of the liver give particular information as regards this but cannot be expected to throw light on the other activities of the organ. In addition Gonzalez and Karr<sup>76</sup> point out that the liver possesses a large factor of safety which precludes the use of any function test to detect minor disturbances of the organ. In view of the multiplicity of the functions of the liver and in view of its powers of regeneration (Rolleston<sup>75</sup>), it is easily understood how this organ may be somewhat diseased while preserving quite well some or all of its functions. Flint's<sup>67</sup> results certainly showed, by means of the van den Burgh test (incidentally he found the laevulose test somewhat more reliable), the majority of his cases of gall-bladder disease to be accompanied by hepatic disturbance. One might question the accuracy of the results as regards the bile pigment content of the blood found in the pathological cases investigated by the writer, but the fact that in the 4 cases of pernicious anaemia to be mentioned later, a condition in which one does expect to find a blood bilirubin value above normal, this was found tends to prove the method used was reliable. It is difficult to explain the different results arrived at by Flint and the writer in this connection: Flint admittedly used the ordinary van den Bergh method, whereas in these investigations the van den Bergh quantitative method was employed: these are however fundamentally the same. To explain the discrepancy in the results one might produce an argument which is specious, i.e. the degree of affection of the livers as regards the bile regulating mechanism was different in both series, being much less or absent in the writer's cases. This explanation is

however weak and cannot be regarded as giving the reason of the different results. The fact stands out that in the cases of disease of the gall-bladder where the bile pigment content of the blood was estimated to ascertain if the liver was affected - as it probably was in most - the van den Bergh quantitative test was not found of any assistance.

#### OTHER CASES INVESTIGATED BY INTUBATION.

It is now intended to make reference to 10 other cases in which bile was obtained from the duodenum by means of intubation: these cases were of different types but not cases of gall-bladder disease. As the numbers of each type are so small, one does not propose to enter into any discussion but merely to state results and perhaps make one or two suggestions.

Kalk<sup>3 & 39</sup> refers to an interesting condition which he terms primary pleiochromie: in this one observes that the liver bile is greater in bilirubin content and therefore darker in colour, than that seen in normal cases. That this is not due to spontaneous contraction of the gall-bladder is shown by the fact that the flow of such bile lasts indefinitely and <sup>is seen</sup> so long as one keeps the tube in the duodenum. According to Kalk this is to be seen in cases of pernicious anaemia, haemolytic jaundice and so-called catarrhal jaundice when the yellow colour of the skin, etc., is decreasing. Retzlaff<sup>77</sup> noted also that the liver bile in cases of haemolytic jaundice has a high pigment content, while Jones<sup>50</sup> also observed that the amount of bile pigment in cases of pernicious anaemia is increased. 4 cases of pernicious anaemia were investigated by duodenal intubation in order to note if such a type of bile could be observed

(neither pituitrin or oil was given in any of the cases):  
the details of these cases will be given in short :-

- 1) F. 42 years: red-cells 950,000 per c.mm.: blood-film typical of pernicious anaemia: bilirubin in blood 1.5 mg.%. On passing the tube into the duodenum dark bile was immediately obtained; the flow continued, and the bilirubin content of the bile varied from 68 to 176 mg.%, being far above the average for this type of bile. This case was catheterized again 7 weeks later (patient had been treated during that period with **Ventriculin**) when the red-cells numbered 3,340,000 per c.mm. and the blood bilirubin was .4 mg.%; the bile obtained on this occasion was of a light lemon colour throughout.
- 2) F. 50 years: red-cells 1,000,000 per c.mm.: film typical of pernicious anaemia: bilirubin in blood - 1.65 mg.%. After passing tube into the duodenum, dark bile having a bilirubin content of 155 to 178 mg.% was obtained.
- 3) F. 52 years: red-cells 1,100,000 per c.mm.: film typical of pernicious anaemia: bilirubin in blood - 1.1 mg.%. In this case very dark bile was obtained after the tube had been passed into the duodenum: one was however unable to estimate the bilirubin content colorimetrically, because an accurate matching of the colours in the standard and trough could not be achieved. The patient was again catheterized after liver treatment had been carried out: the red-cells then numbered 3,000,000 per c.mm. and the bile obtained was of a dark lemon colour (28 mg.%) : bilirubin in blood .2 mg.%.
- 4) M. 57 years. This case was interesting: the patient had been previously in hospital, and all that was then discovered was that he had a degree of anaemia which was not definitely of the pernicious type. His blood bilirubin was at that time .7 mg.%, and the bile obtained by simple

catheterization was of a lemon colour throughout. He was again admitted to hospital some months after and was definitely worse: on this occasion the blood-film was typical of pernicious anaemia, the red-cells numbered 1,210,000 per c.mm. and the bilirubin content of the blood was 1.3 mg.%. The bile obtained this time by intubation was dark, the highest bilirubin value being 102 mg.%.

2 cases of secondary anaemia were similarly investigated in order to note if the bile obtained offered any contrast to that observed in the above 4 cases.

1) F. 32 years: patient had recently given birth to a child: blood-film typical of secondary anaemia: red-cells numbered 1,200,000 per c.mm. and bilirubin in blood was .25 mg.%. After the tube had been passed into the duodenum a light lemon-coloured bile was obtained. Patient recovered quickly on iron.

2) F. 40 years: anaemia following severe uterine haemorrhage: film showed secondary anaemia: red-cells were 1,050,000 per c.mm. and blood-bilirubin .45 mg.%. On duodenal intubation a continuous flow of lemon bile - bilirubin content 16 mg.% - was observed.

As said before, it is not intended to discuss the findings in these cases. It is recognized that in anaemia of the pernicious type the liver shows pigment changes and one would point out the obvious differences in the pigment content of the liver bile obtained in pernicious and secondary anaemias. Perhaps this could be utilised either to complete the diagnosis of anaemias of the pernicious type or to assist in the making of a diagnosis where the type of anaemia present is, as at times occurs, doubtful. One interesting feature seen in these cases of pernicious anaemia is, that, as the blood condition improves, the liver bile approximates in bilirubin value to the normal.



4 cases of so-called catarrhal jaundice were investigated by duodenal catheterization: the intubation was carried out in 3 of them when the jaundice was at its height, so far as could be determined clinically (again neither pituitrin or oil was given).

1) M. 26 years. After passing the tube into the duodenum, bile of a light lemon colour was obtained: the amount averaged 3 cc. per 5 minutes.

2) M. 33 years. The bile obtained in this case was plentiful, being well above the amount usually obtained: it averaged 11.5 cc. per 5 minutes and was of a light lemon colour. On repeating the intubation when the jaundice was definitely less, marked dark bile was obtained, the bilirubin content varying from 60 to 80 mg.‰.

3) M. 40 years. Bile of average amount was obtained: it was of a light lemon colour.

4) M. 62 years. This case was admitted to hospital after the jaundice had been present for some time: duodenal intubation was undertaken some time after admission, when the icteric tinge was definitely less, and the bile so obtained was darker than normal throughout, the highest bilirubin values being 55 and 60 mg.‰.

These cases were investigated to discover if any bile could be obtained by duodenal catheterization and to verify, if possible, Kalk's opinion that cases of simple jaundice - as he terms them - have a darker liver bile than normal as they improve. It has been the teaching for many years that so-called catarrhal jaundice is a condition in which the jaundice is the result of obstruction of the mouth of the common duct by swollen mucous membrane and thick mucus arising from catarrh of the biliary papilla: this condition is held to be the result of gastro-duodenal catarrh with

spreading of the inflammation for a short distance up the common duct. Lyon<sup>40</sup> refers to the condition as catarrhal jaundice and holds that the icterus disappears rapidly with biliary drainage after the removal of the mucus causing the obstruction, from the common-duct. Dicks<sup>10</sup> in 2 cases of catarrhal jaundice, which he catheterized, believed he saw, in the bile obtained, the plugs of mucus which had caused obstruction of the common duct. On the other hand Franck,<sup>78</sup> as regards catarrhal jaundice, holds that the old idea of gastro-duodenal catarrh causing obstruction of the common duct by mucus with consequent mechanical jaundice is fallacious, and he would place the condition, at least in many cases, in the class of liver disease where the parenchyma is affected. He sees in so-called catarrhal jaundice an early and mild stage of acute necrosis of the liver. This view is confirmed by the recent investigations of Swedish workers, who have commented on the comparative frequency of cases which begin as catarrhal jaundice and die later of liver necrosis. Lepehne<sup>79</sup> also holds the view that catarrhal jaundice is a mild acute hepatitis and not due to catarrhal obstruction as was so long believed. The cases of so-called catarrhal jaundice investigated here are, of course, far too few for any definite deductions to be made from them, but in 3 of them it was seen that at the height of the jaundice (so far as could be judged clinically), there was no impediment to the outflow of bile from the common duct: incidentally plugs of mucus similar to those observed by Dicks were not seen in any of these cases. In 2 of the cases, by the use of catheterization on 2 occasions, one was able to confirm Kalk's views that in so-called catarrhal jaundice, when the jaundice is clearing, the liver bile has a higher bilirubin content than normal.

S U M M A R Y.

The investigation of 25 normal cases by biliary drainage, using the method employed by Kalk with certain modifications, shows that not only is pituitrin capable of causing emptying of the gall-bladder, but its use is, in combination with olive oil, a means of arriving at the decision that the organ can concentrate and expel the bile it receives from the liver and that the cystic duct is patent. One is however unable to agree with Kalk and Schöndube that pituitary extracts are absolutely reliable cholekinetic agents: one takes the view held by Held and Goldbloom that pituitrin (the most reliable of pituitary extracts) does not in every case with a normal gall-bladder bring about contraction of the organ with expulsion of its contents. This applies also to other substances used for this purpose, e.g. magnesium sulphate, peptone, but pituitrin is at least as reliable and has definite advantages over these and is the cholekinetic agent of choice in biliary drainage: it should be followed by the administration of olive oil when it fails to produce any or full response on the part of the organ.

The majority of normal gall-bladders contain, after a period of fasting, bile of a bilirubin value of over 90 - 100 mg.%, but on occasion the bile-bilirubin in the normal organ at such a time does not reach this figure: this is not in accordance with the views held by Kalk and Schöndube.

As a means of assessing the function of the pathological gall-bladder, pituitrin and olive oil are of definite value. The results of biliary drainage so employed in this series of pathological cases were, if one accepted the normal standard for bilirubin content of the gall-bladder bile set by Kalk and Schöndube, more reliable in assisting in the

function-diagnosis than were Kalk's. Even if not accepting this standard - it has not been accepted in these investigations - they compare well with his results. It was found that the ~~causes~~ causes of no response of the gall-bladder to pituitrin and oil or of the expelled bile having a comparatively low bilirubin content are obstruction of the cystic duct or changes in the wall of the organ. This agrees with Kalk's findings.

The examination of the sediment of the bile obtained from the gall-bladder in 1<sup>1</sup> pathological cases after the use of pituitrin was of no assistance in the diagnosis of the particular lesion of the organ. This is not in accordance with the views held by Kalk, but the number of cases so investigated is small, and it is questionable if much or any weight can be laid on the results.

The method of arriving at a decision regarding hepatic involvement in gall-bladder disease, by means of the colorimetric estimation of bile pigment in the blood, was of no real help in these investigations. This is also not in agreement with Kalk's views.

The opinions of Kalk regarding the presence of a high bilirubin content in the liver bile in pernicious anaemia were confirmed in the 4 cases investigated: the possibility is raised of this finding being of use in distinguishing anaemias of the pernicious type from others and in the confirming of the diagnosis in this condition. The occurrence of this phenomenon also in cases of so-called catarrhal jaundice, when the icterus was disappearing, was observed: in addition no difficulty was experienced in obtaining bile from the common-duct in such cases when the jaundice was clinically at its height. (One admits that the number of cases investigated is small.)

According to the results obtained in these investigations, duodenal catheterization with the use of pituitrin

and olive oil is of definite assistance in the diagnosis of gall-bladder lesions in so far as they affect the function of the organ. To utilize it to the full however it should be combined with an accurate history and careful clinical investigation of the patient, together possibly with a reliable method of cholecystography. One would suggest it occupy perhaps the place in investigation of the gall-bladder that the test-meal has in investigation of the stomach. As with the test-meal, however, biliary drainage, irrespective of the cholekinetic substances employed, as a test of gall-bladder function, is of value only in suggesting or confirming a diagnosis, and the latter certainly cannot - and should not - stand or fall by the results obtained by it alone.

APPENDIX.

(Details of the pathological cases investigated are given here briefly.)

OPERATED CASES.

1) M. 64 years. Repeated attacks of pain in right hypochondrium, lasting 2 - 4 days: said to have been jaundiced after one of these attacks.

Examination :- Slight rigidity over gall-bladder area: tender on pressure in this region: hyperaesthesia noted here also.

Bilirubin in blood - .8 mg.‰.

Duodenal intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Gall-bladder full of pus: no stones: wall very much thickened and densely adherent to surrounding tissues: gall-bladder removed. Died later.

Pathological report :- Gangrenous cholecystitis superimposed on chronic cholecystitis.

2) F. 57 years. Recurrent attacks, for 4 months, of pain in right upper abdomen: pain radiated through to scapular region.

Examination :- Slight icteric tinge of sclerotics: tender on pressure in region of 9th right costal cartilage.

Bilirubin in blood - 1.6 mg.‰

Duodenal catheterization :- Dark bile obtained after pituitrin: highest bilirubin value - 50 mg.‰: oil caused no response.

Operation :- 3 stones, of size of peas, found in common duct with biliary sand: gall-bladder small with thick wall and adherent somewhat to intestines.

3) F. 52 years. 1st attack of pain in right hypochondrium: pain radiated round to back and later through to angle of right scapula: still later radiated to appendix region.

Examination :- Tender on deep pressure in gall-bladder region: slight rigidity in this area.

Duodenal intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Numerous small stones found in gall-bladder: cystic duct obstructed by stones: gall-bladder thick and fibrous and adherent to mesocolon.

4) F. 47 years. 3 attacks of pain in right hypochondrium: pain radiated round to back and in last attack down right arm: Hyperaesthesia in gall-bladder region noted by patient after last attack.

Examination :- Slightly tender on deep pressure over gall-bladder: little hyperaesthesia in this region.

Bilirubin in blood - .3 mg. %.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- 2 large stones found in gall-bladder with mucus like substance of very tough consistency: another stone found impacted in upper part of cystic duct, producing distention and obstruction. Gall-bladder wall thick and fibrous and adherent to liver.

5) F. 52 years. 1st attack of pain in epigastric and umbilical regions: pain radiated through between scapulae.

Examination :- Tumour as large as medium sized orange palpable between xiphisternum and umbilicus, most of it situated to right of mid-line: marked tenderness over tumour: slightly tender on pressure in gall-bladder region: degree of rigidity in latter area.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Pancreas found enlarged and very hard: areas of fat necrosis seen in omentum: gall-bladder small with hard, thickened wall: 2 stones impacted in cystic duct.

6) F. 49 years. Repeated attacks of pain in right upper abdomen: pain radiated through between scapulae: 1st attack 14 years before.

Examination :- 3 areas of tenderness to pressure over abdomen - 1 over gall-bladder, 1 in appendix region and 1 - the most marked - midway between xiphisternum and umbilicus.

Duodenal catheterization:- Dark bile was obtained after pituitrin: highest bilirubin value - 74 mg.‰: no dark bile obtained after oil.

Operation :- 5-stones found in gall-bladder: 2 of them joined together to fill gall-bladder almost completely: wall of gall-bladder somewhat thickened.

7) F. 58 years. Recurring attacks of slight pain in left hypochondrium and epigastrium: at times pain radiated through to back.

Examination :- Slight tenderness on pressure all over abdomen: most marked in region of 9th left costal cartilage.

Bilirubin in blood - .5 mg.‰.

Intubation :- dark bile obtained after pituitrin: highest bilirubin value - 73 mg.‰: dark bile obtained also after oil: highest bilirubin value - 138 mg.‰.

X-ray (without contrast filling) - numerous small opacities in region of gall-bladder.

Operation :- Numerous small stones in gall-bladder: gall-bladder appeared fairly normal.

Histological report (on gall-bladder) :- "Wall of gall-bladder shows signs of slight cholecystitis with submucous fibrosis: mucous membrane somewhat atrophied and catarrhal."

8) F. 57 years. 2nd attack of pain in right upper abdomen.

Examination :- Tender along margin of ribs on right side, especially in anterior axillary line: slight rigidity in gall-bladder region.

Bilirubin in blood - .4 mg.‰.



Duodenal catheterization :- No dark bile obtained after pituitrin and oil.

Operation :- Gall-bladder buried in mass of adhesions: omentum puckered round it : fundus of bladder gangrenous with perforation -  $\frac{1}{2}$  inch in diameter - at tip. Gall-bladder large and full of pus with numerous small stones: large stone firmly impacted in the cystic duct, obstructing it: wall of gall-bladder very much thickened in parts.

9) F. 53 years. Operated on 14 years previously for, as patient said, gall-stones: nature of operation not discovered. 1 year previously vomited bile frequently: became, so patient said, jaundiced: 2 months before admission had attack of vomiting and was jaundiced for 1 week: has vomited since after meals: no marked pain - little over old scar.

Examination :- Slightly tender in region of 9th right costal cartilage: degree of hyperaesthesia in this region.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- No gall-bladder found: had been removed at previous operation: nothing else abnormal found.

10) F. 31 years. Recurrent attacks of pain for 5 years in right upper abdomen: pain radiated, at times, round to right scapular region: after attacks was slightly jaundiced (so patient said) for few days.

Examination :- No tenderness, etc., found anywhere over abdomen.

Bilirubin in blood - .3 mg.‰.

Duodenal catheterization :- Dark bile obtained after pituitrin: highest bilirubin value - 65 mg.‰: no dark bile obtained after oil.

Operation :- 2 large and 12 small stones found in gall-bladder: cystic duct contained no stones: wall of gall-bladder somewhat thickened.

11) M. 55 years. 2nd attack of pain in right hypochondrium: on both occasions pain radiated through to back, between scapulae. Was in hospital during 1st attack: became slightly jaundiced.

Examination :- Tender on deep pressure over gall-bladder. Bilirubin in blood - .8 mg.%.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Gall-bladder wall very much thickened and densely adherent to liver and duodenum: several stones in gall-bladder: cystic duct dilated and obstructed by stones: gall-bladder excised: died later.

12) F. 58 years. Frequent attacks of pain in gall-bladder region for 7 years: at times pain radiated between scapulae: said to have been slightly jaundiced after 1st attack.

Examination :- Slightly tender to pressure in gall-bladder area.

Bilirubin in blood - .3 mg.%.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Large distended gall-bladder found: 1 large and several small stones in gall-bladder: wall rather soft: cystic duct clear of stones.

13) F. 55 years. 2nd attack of pain in right hypochondrium: vomited during attacks: pain on both occasions travelled through between scapulae and to right shoulder region.

Examination :- Tender on pressure in gall-bladder region.

Duodenal catheterization :- Dark bile obtained after pituitrin: highest bilirubin value - 65 mg.%. Dark bile obtained also after oil: highest bilirubin value - 47 mg.%.

Operation :- Slightly enlarged, soft-walled gall-bladder found: no stones: cholesterin-sand present in

gall-bladder: wall of gall-bladder typical of chronic cholecystitis.

14) M. 40 years. Recurrent attacks of pain in right upper abdomen with vomiting: pain radiated to left across epigastric region.

Examination :- Mass palpable to right of umbilicus: surface irregular: very tender to pressure. Slightly tender in region of 9th right costal cartilage.

Bilirubin in blood - .4 mg.‰.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- 1 large stone found lying partly in neck of gall-bladder and partly in cystic duct: cystic duct obstructed by stone: gall-bladder wall fibrous and thickened: mucous membrane of bladder very friable. Palpable mass was omental abcess: gall-bladder behind and above it.

15) F. 44 years. Operated on  $4\frac{1}{2}$  months previously for attacks of pain in right hypochondrium: 20 stones removed from gall-bladder which was drained: free from symptoms for 2 months. Since then frequent attacks of pain in gall-bladder area: pain travelled down to appendix region and through to angle of right scapula.

Examination :- Tender on pressure over gall-bladder: also midway between xiphisternum and umbilicus: slight hyperaesthesia in gall-bladder region.

Bilirubin in blood - .7 mg.‰.

Duodenal catheterization :- No dark bile obtained after pituitrin and oil.

Operation :- Gall-bladder moderately distended: mucous membrane appeared healthy: stone firmly impacted in cystic duct, obstructing it.

(This case is interesting: because of the history and the findings obtained by biliary drainage, the writer raised the possibility of a stone having been left in the cystic duct

at previous operation: surgeon however made a diagnosis of pancreatitis, as he was certain he had removed all stones from the gall-bladder and ducts at earlier operation.)

16) F. 37 years. 3 attacks of pain in right upper abdomen, lasting 3-4 days: pain radiated through between shoulders.

Examination :- Tender on deep pressure in gall-bladder area: slight hyperaesthesia in this region.

Intubation :- No dark bile obtained after pituitrin and oil.

Cholecystography :- No filling of gall-bladder seen.

Operation :- Shrunken gall-bladder found: wall fibrous: 8 small stones and 1 large one found in gall-bladder: cystic duct obstructed by stone: gall-bladder excised: anaesthetic death.

17) F. 55 years. For 15 years attacks of pain in right hypochondrium: pain travelled at times to right shoulder and left breast.

Examination :- Tender to pressure over gall-bladder: tender also in mid-line between xiphisternum and umbilicus: slight rigidity in latter area.

Bilirubin in blood - .4 mg.‰.

Duodenal intubation :- After pituitrin dark bile was obtained: highest bilirubin value - 136 mg.‰.

Operation :- Numerous small stones found in gall-bladder: wall seemed fairly normal.

Histological report (on gall-bladder wall) :-

"Gall-bladder presents relatively normal appearance."

18) F. 53 years. Indefinite history of pain in epigastrium: said to have been jaundiced previous year after attack of pain: pain on that occasion associated with vomiting: present attack lasted 3 weeks: occasional pyrexia in hospital.

Examination :- Tender on pressure in gall-bladder region.

X-ray (cholecystography) - No filling of gall-bladder.

Intubation :- No dark bile obtained after pituitrin and Oil.

Operation :- Abdomen full of fluid: no gall-bladder found: died later.

Autopsy :- General inflammatory condition of peritoneum: no gall-bladder found: cystic duct lying free at gall-bladder end: carcinoma of cystic duct found: inflammation of gall-bladder: gall-bladder sloughed off.

19) F. 45 years. 1st attack of pain in right upper abdomen: pain radiated to right shoulder region and down right arm.

Examination :- Tender on pressure over gall-bladder: hyperaesthesia in this region: tender also in right supra-scapular region.

Bilirubin in blood - .3 mg.‰.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Acute inflammation of gall-bladder: numerous small stones in gall-bladder.

20) F. 53 years. Repeated attacks of pain in right upper abdomen: pain radiated in each attack between scapulae: on last occasion also to right shoulder region. Vomited during attacks: first attack said to have been followed by jaundice.

Examination :- Slight icteric tinge of sclerotics: exquisitely tender on pressure over gall-bladder region: hyperaesthesia across abdomen, between lower margins of ribs and umbilicus. Liver seemed harder than normal.

Bilirubin in blood - 2.25 mg.‰.

Duodenal catheterization :- No dark bile obtained after pituitrin: dark bile obtained after oil: dark bile flow lasted only 5 minutes: bilirubin value of this bile - 68 mg.‰.

Operation :- 1 stone in gall-bladder: wall of gall-bladder thickened and adherent somewhat to surrounding structures: 2 stones in cystic duct: not firmly impacted, being moveable.

21) F. 38 years. 6 years previously attack of pain in right upper abdomen: free for 5 years: in last year frequent attacks of pain in right hypochondrium: pain travelled at times to back - between scapulae - and to left shoulder region.

Examination :- Tender on pressure over region of 9th right costal cartilage: hyperaesthesia in this area.

X-ray (cholecystography) :- 2 opacities, suggesting stones in gall-bladder, seen.

Intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Gall-bladder appeared healthy: steel blue colour: no stones felt or seen: dark bile present in gall-bladder: bilirubin content of this bile - 442 mg.‰.

Histological report (on piece of gall-bladder wall removed):-

"Chronic and subacute cholecystitis present."

Bacteriological report :- "Pure growth of streptococci obtained from section of wall."

22) F. 48 years. Recurrent attacks of pain in gall-bladder region: vomited in some of attacks.

Examination :- Tender on pressure in gall-bladder area.

Duodenal intubation :- No dark bile obtained after pituitrin and oil.

Operation :- Large stone occupying practically whole of gall-bladder: mucous membrane of gall-bladder inflamed.

23) F. 65 years. Frequent mild attacks of pain in right hypochondrium: pain radiated between shoulders.

Examination :- Tenderness on pressure in gall-bladder region: slight continuous pyrexia.

Intubation :- no dark bile obtained after pituitrin and oil.

Operation :- gall-bladder was sloughing mass: pus present in gall-bladder: died later.

UNOPERATED CASES.

1) F. 28 years. Frequent attacks of pain for 5 months in right hypochondrium: recently gave birth to child: after last attack before delivery became, so she said, jaundiced: 2 attacks after delivery: pain radiated in last attack between scapulae and to region of right shoulder: vomited in attacks.

Examination :- Extremely tender over gall-bladder: rigidity in this region: hyperaesthesia also.

Bilirubin in blood - .3 mg.‰.

Duodenal intubation :- No dark bile obtained after pituitrin and oil.

2) F. 50 years. 2 attacks of pain in gall-bladder region: in last attack pain travelled through to back - between scapulae.

Examination (on admission) :- Slightly tender on pressure in region of 9th right costal cartilage: little rigidity in this region: slightly jaundiced.

Bilirubin in blood (not estimated till icterus had gone) - .4 mg.‰.

Intubation (also not done till icterus gone) :- Dark bile obtained after pituitrin: highest bilirubin value - 50 mg.‰: no dark bile obtained after oil.

3) F. 40 years. Numerous attacks of pain in right upper abdomen with vomiting: in 1st attack pain very severe: travelled between scapulae: said to have been jaundiced after 1st attack.

Examination (on admission) :- Tender on pressure over gall-bladder: rigidity and slight hyperaesthesia in this region: indefinite swelling felt in gall-bladder area.

Bilirubin in blood - .7 mg.‰.

X-ray (cholecystography) :- No filling of gall-bladder.

Duodenal catheterization (done 12 days after admission):-

No dark bile seen after pituitrin and oil.

4) F. 52 years. Referred from surgeon as case of gall-bladder disease unfit for operation: repeated attacks of pain in right hypochondrium for 4 years: pain very severe: vomited in attacks.

Examination :- Tenderness on pressure in gall-bladder region.

Bilirubin in blood - .4 mg.%.<sup>s</sup>.

Cholecystography :- Faint filling of gall-bladder.

Intubation :- Dark bile obtained after pituitrin: flow of this bile lasted only 5 minutes: bilirubin content - 45 mg.%.<sup>s</sup>: no dark bile obtained after oil.

(Treated with magnesium sulphate, olive oil, atropine and pituitrin injections: much improved after 10 days treatment: tenderness in gall-bladder region much less.)

5) F. 63 years. Attack of severe pain in right upper abdomen: began some days before admission: on admission extremely tender over gall-bladder: rigidity and hyperaesthesia in this region: some pyrexia (Ward journal).

Examination (made 12 days after admission) :- Tenderness in gall-bladder region: slight hyperaesthesia.

Bilirubin in blood - .4 mg.%.<sup>s</sup>.

Duodenal catheterization (done 12 days after admission):- dark bile obtained after pituitrin: highest bilirubin value - 51 mg.%.<sup>s</sup>: dark bile obtained also after oil: highest bilirubin value - 313 mg.%.<sup>s</sup>.

6) F. 58 years. Repeated attacks of pain for 9 months in gall-bladder region: pain radiated between shoulders: vomited during attacks. Operated on 8 years previously: cholecystotomy done then (report from hospital where operation done). Examination :- Marked tenderness over gall-bladder: slight rigidity in this area.

Intubation :- No dark bile obtained after pituitrin: dark bile obtained after oil: highest bilirubin content - 50 mg.%.<sup>s</sup>.



7) F. 47 years. 3 attacks of pain in right upper abdomen: colicky<sup>k</sup> in nature with vomiting. Had typhoid fever twice - at age of 17 and 31 years.

Examination :- Tender on pressure in gall-bladder region: hyperaesthesia in this area.

Intubation :- No dark bile obtained after pituitrin and oil.

Widal - slightly positive for bacillus typhosus: no growth obtained from bile and faeces.

8) F. 56 years. Repeated attacks of pain in gall-bladder region: pain radiated between scapulae: 2 milder attacks of similar nature in hospital: pain in one travelled to region of right shoulder.

Examination :- Tenderness over gall-bladder.

X-ray (of stomach and duodenum) :- "duodenum shows some deformity due probably to adhesion to gall-bladder."

Duodenal intubation :- No dark bile obtained after pituitrin and oil .

9) F. 37 years. 2 attacks of pain in right hypochondrium: vomited: pain radiated in 2nd attack to angle of right scapula.

Examination :- Tenderness on pressure in gall-bladder region: slight rigidity and hyperaesthesia in this area.

Bilirubin in blood - .5 mg.‰.

Intubation :- Dark bile obtained after pituitrin: highest bilirubin value - 49 mg.‰.: dark bile obtained also after oil: highest bilirubin value - 40 mg.‰.

10) F. 57 years. Frequent attacks of pain in right upper abdomen with vomiting: own doctor noted degree of jaundice after one attack.

Examination :- Slightly tender on pressure over gall-bladder: slight rigidity in this region.

Duodenal catheterization :- No dark bile obtained after pituitrin and oil.

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