Resistance of staphylococci to erythromycin developed readily *in vitro* but appeared to follow the "stepwise" pattern of acquired resistance to penicillin rather than that of streptomycin. From the experiments described above it would appear that a culture of a sensitive strain of staphylococcus may contain spontaneous mutants which are more resistant to erythromycin. Mutants resistant to high levels of erythromycin were not found in these experiments. However, by serial subculture on media containing erythromycin progressive increase of resistance occurred in 14 strains of staphylococci tested. These strains differed from each other in the speed of development of resistance, but in no case was the first "step" to a resistance more than four times that of the original strain. Apart from some reduction in rate of growth, the biological characteristics and phage pattern of the resistant variants were unchanged. Haight and Finland (1952e) observed that development of resistance was associated with loss of coagulase activity. This finding has not been confirmed in the present study or by later experience of the same group of workers (Purcell *et al.*, 1953). Resistant variants were not found to have developed cross-resistance to any other antibiotic except carbomycin. Similar experiences have been reported by Haight and Finland (1952e) and Finland *et al.* (1952). The fact that originally sensitive strains of staphylococci rapidly develop resistance *in vitro* and also *in vivo* (McGuire *et al.*, 1952) is a potential drawback to the use of erythromycin. However, recent work (Purcell *et al.*, 1953) shows that *in vitro* combinations of erythromycin with penicillin or with streptomycin will delay or depress the emergence of resistance to both erythromycin and penicillin or streptomycin.

Summary

Methods for sensitivity testing of staphylococci with erythromycin are described. Factors affecting these tests are discussed.

The sensitivity to erythromycin of a large series of strains of *Staph. aureus* is shown to be of the order of 0.5 µg./ml., and to be independent of their phage type or their behaviour to four other antibiotics.

The effect of erythromycin on the growth rate of staphylococci has been shown to vary according to the concentration of antibiotic. Concentrations above the minimum inhibitory concentration produce a fall in the number of viable organisms.

The development in staphylococci of resistance to erythromycin appears to follow a stepwise pattern resembling that seen with penicillin.

Resistant staphylococci were found to differ from the erythromycin-sensitive parent organism only by slight differences in growth rate and by the acquisition of cross-resistance to carbomycin.

My thanks are due to Dr. R. E. O. Williams, Staphylococcal Reference Laboratory, Central Public Health Laboratory, Colindale, for performing phage-typing on the strains of *Staph. aureus* used in the resistance experiments.

REFERENCES

- Barber, Mary (1953). *J. gen. Microbiol.*, **8**, 111.
 Demerec, M. (1948). *J. Bact.*, **56**, 63.
 English, A. R., Field, M. F., Szendy, Sophia R., Tagliani, Nancy J., and Fitts, R. A. (1952). *Antibiot. and Chemother.*, **2**, 678.
 Finland, M., Wilcox, Clare, Wright, S. S., and Purcell, E. M. (1952). *Proc. Soc. exp. Biol., N.Y.*, **81**, 725.
 Haight, T. H., and Finland, M. (1952a). *Ibid.*, **81**, 175.
 — (1952b). *Ibid.*, **81**, 188.
 — (1952c). *New Engl. J. Med.*, **247**, 227.
 — (1952d). *Amer. J. clin. Path.*, **22**, 806.
 — (1952e). *Proc. Soc. exp. Biol., N.Y.*, **81**, 183.
 Heilman, F. R., Herrell, W. E., Wellman, W. E., and Geraci, J. E. (1952). *Proc. Mayo Clin.*, **27**, 285.
 Knox, R., King, M. B., and Woodroffe, R. C. (1952). *Lancet*, **2**, 854.
 Luria, S. E., and Delbrück, M. (1943). *Genetics*, **28**, 491.
 McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E., Flynn, E. H., Powell, H. M., and Smith, J. W. (1952). *Antibiot. and Chemother.*, **2**, 281.
 May, J. R., and Morley, C. W. (1952). *Lancet*, **1**, 636.
 Miles, A. A., Misra, S. S., and Irwin, J. O. (1938). *J. Hyg., Camb.*, **38**, 732.
 Purcell, E. M., Wright, S. S., and Finland, M. (1953). *Proc. Soc. exp. Biol., N.Y.*, **82**, 124.
 Tanner, F. W., jun., English, A. R., Lees, T. M., and Routien, J. B. (1952). *Antibiot. and Chemother.*, **2**, 441.

SOME LESSONS FROM 4,000 UTERO-TUBAL INSUFFLATIONS*

BY

ALBERT SHARMAN, M.D., D.Sc., Ph.D.

F.R.C.O.G.

Senior Assistant Surgeon, Royal Samaritan Hospital for Women, Glasgow

Personal experience of just over 4,000 utero-tubal insufflations has taught several practical lessons. The foremost lesson, in my opinion, concerns the gas employed and its safety.

Rubin's Test

Utero-tubal insufflation was first described by Rubin in 1920, so that more than 30 years have elapsed to permit the evaluation of a large number of these tests by investigators all over the world and the accumulation of recorded complications and untoward sequelae. It must not be overlooked, of course, that details of mishaps and even fatalities might pass unpublished. An illustration of this is to be found in the report of the meeting of the Section of Obstetrics of the Royal Academy of Medicine in Ireland on November 7, 1947, in which a speaker made the bald statement that he knew of eight deaths in Ireland following the Rubin test. Nevertheless, a study of the replies to Rubin's (1947) detailed questionnaire, returned by 356 gynaecologists and involving 80,376 insufflations, must supply the data to answer the more important questions, including the safety of the procedure. Among all these insufflations, embolism occurred in 15 patients, of whom 3 died. These deaths are additional to the 10 known post-insufflation deaths from embolism reported in the literature; Frommolt (1925), 1 case; Moench (1927), 2 cases; Mansfeld and Dudits (1934), 1 case; Weitzman and Cohen (1937), 1 case; Dible *et al.* (1938), 1 case; Feiner (1942), 1 case; Finn (1945), 1 case; and Faulkner (1946), 2 cases. In all these fatal cases air or oxygen was used; in no instance is there a record of death from embolism following insufflation with carbon dioxide. Non-fatal but alarming clinical effects, in varying degrees, have been observed by many investigators, but these are rarely seen with the use of carbon dioxide.

At the Royal Samaritan Hospital for Women, Glasgow, insufflation has been employed for nearly 25 years, and at no time has any gas other than carbon dioxide been used. The test has been carried out by various members of the staff on an aggregate of over 6,500 occasions. My personal share of these experiences amounts to just over 4,000 insufflations. None of us has seen any evidence of embolism and there certainly has been no fatality. It is reasonable, therefore, to conclude from accumulated clinical experience that carbon dioxide is the gas of choice. Moreover, it must be pointed out that Rubin, in more than 10,000 insufflations personally carried out, with the exception of approximately the first 100 cases in which he used oxygen (a procedure which was quickly abandoned by him because of the disadvantage that it takes 24–100 hours to be absorbed from the peri-

*The basis of a lecture given to Greenock and District Faculty of Medicine on March 3, 1953, at Greenock Royal Infirmary.

toneal cavity), has never used any other gas than carbon dioxide, which is rapidly absorbed. The designation "Rubin test" therefore implies the use of carbon dioxide gas only. Air has the same disadvantages as oxygen—namely, its slow absorbability and its potentiality of producing embolism, as shown in the cases outlined above. In addition, it presents a greater theoretical danger of introducing infectious material. On several occasions I have introduced varying quantities of carbon dioxide, from different types of insufflator, direct into broth culture medium; on no occasion was any bacterial growth obtained. In this connexion it may be observed that in Rubin's questionnaire a total of 190 pelvic infections followed the 80,376 insufflations. Of these, 38 required operative treatment. There were two deaths, both in patients in whom air had been insufflated. I have had five pelvic infections in over 4,000 insufflations with carbon dioxide. Three were mild and two severe; one of the latter required operation. Not one was fatal.

Use of Air in Insufflation

It is of interest to retrace briefly the steps by which air came to be introduced for the purpose of insufflation. Furniss (1921) reported a simplification of the Rubin test and suggested that the method might be still further simplified by using air instead of carbon dioxide. Jacoby (1923), acting on this suggestion, was the first to report the use of air. He claimed that it had the following advantages: it eliminated the necessity for having on hand cumbersome tanks of gas with other attachments; there was no possibility of air being exhausted, as occasionally happens with tanks when a test is in progress; being more compact, the apparatus is readily portable should occasion arise; there is no expense or inconvenience in replacing tanks; the air is free and always obtainable. In 40 cases Jacoby found no evidence of any serious infection, and added that there is no reason to expect infection as a result of the introduction of air, since in every laparotomy air enters the peritoneal cavity with no untoward results. In the following year Victor Bonney (1924) described his simplified air apparatus, involving the use of a cannula, of the size of a No. 7 dilator, and a manometer. He stated that it had been previously pointed out to him by Arthur Gray that an elaborate apparatus was not necessary and that equally reliable results could be obtained by injecting air by means of a simple rubber bulb, attached to which was a metal tube furnished with a rubber obturator.

It is obvious, therefore, that air was introduced for insufflation solely for the purpose of simplification of procedure, which meant, essentially, the elimination of the necessity for a bulky cylinder of carbon dioxide or oxygen and a heavy and not easily portable apparatus. To-day, this reason is not valid, since several types of portable insufflation apparatus employing carbon dioxide are available. Moreover, Jacoby's argument that the use of air must be safe, as it enters the peritoneal cavity at every laparotomy, is fallacious, since in utero-tubal insufflation the circumstances are very different. In the latter procedure air is forced under positive pressure into the uterine cavity, from which it can escape only through the tiny tubal lumina and not even therefrom in cases of non-patency. The circumstances are not the same, however, in Decker's test of tubal patency, in which a uterine cannula is introduced when the patient adopts the knee-chest position: air then enters under negative pressure. According to Finn (1945), the two prerequisites for the development of an air embolism are (1) a vessel which is in a state of incomplete collapse, and (2) the introduction of air under positive pressure into the circulation. These conditions are present, in varying degree, in tubal insufflation with air, especially when associated with curettage. The embolism is of the venous type, air entering

the peripheral veins and flowing by means of the vena cava to the right side of the heart and thence to the pulmonary arteries.

Further consideration of the possibility that in utero-tubal insufflation the gas used might enter the blood stream via uterine veins may now be given on the lines of accepted physiological fact and also on experimental lines. On general physiological principles, air (with its high nitrogen content) is thoroughly dangerous; oxygen is less dangerous because of the affinity of haemoglobin with the gas, and carbon dioxide infinitely the safest. The solubilities of nitrogen, oxygen, and carbon dioxide in millilitres per 100 ml. of blood at 38° C. and 760 mm. of mercury pressure are 1.1, 2.3, and 54.1 respectively (Samson Wright, 1945). Indeed, owing to the high capacity of blood for carbon dioxide it is generally accepted by physiologists that it must be almost impossible to produce carbon dioxide embolism. It is well known that the latter gas is rapidly absorbed and eliminated through the lungs. This rate of absorption is probably as high as 250 ml. per minute (Van Slyke and Gross, quoted by Rubin, 1947). It should be noted, also, that in transuterine pneumoperitoneum (Petersen), for visualizing intrapelvic organs on an x-ray film, it is customary to introduce as much as 1,000 ml. of carbon dioxide into the abdominal cavity; this procedure causes only moderate discomfort.

Air Embolism

Experimentally, air embolism has been studied by several investigators. As early as 1667, Ride produced death in cattle by blowing air under pressure into their jugular veins. Jung and Pierre (1935) reported, in their findings in experiments in dogs, that when air is injected in large quantities into the systemic veins death is due to the filling of the right side of the heart with air. Lenggenhager (1936), as a result of animal experiments with air, came to the conclusion that death is due to blocking of the pulmonary artery and arrest of the pulmonary circulation. Richardson *et al.* (1937) found that there was no constancy in the lethal amount of air required, even in individuals of the same species. They estimated that about 500 ml. of air would be required to kill a human being, basing their inferences on experimental air embolisms produced in small animals. Beauchesne, in 1818, during the removal of a neck tumour, observed the first recorded case of air embolism in the human—an effect of suction produced by negative venous pressure, as later indicated by Finn.

I have conducted numerous experiments introducing air, oxygen, and carbon dioxide into the blood streams of rabbits, with the following conclusions: if one minute is taken to inject each gas the large majority of rabbits will die almost immediately with 3 ml. of air and with 4 ml. of oxygen; most of them suffer no ill effects with 15 ml. of carbon dioxide, although larger amounts can be fatal. A fatal effect from carbon dioxide can also be produced if the rate of flow of the gas is increased—for example, 30 ml. in half a minute. Immediate necropsy of the heart of the rabbit injected with air shows the right side filled with frothy blood; examination of the brain reveals air bubbles in the capillaries. It is of interest to note that the necropsy in the cases of Moench and of Dible *et al.* showed the right auricle and ventricle to be filled with "frothy air" and, in the case of Finn, revealed "25 ml. of air in the right ventricle and pulmonary arteries."

There is therefore clear evidence on clinical, physiological, and experimental grounds that insufflation with air is potentially dangerous. It may be true, as Dible *et al.* state, that the risk of air embolism could probably be abolished in tubal insufflation if the amount of air were carefully measured and never allowed to exceed a total of 100 ml., and there is no doubt that several thousand insufflations with air have been performed without ill effect or fatality by many careful investigators all over the world. Nevertheless, the great safety of carbon dioxide makes it uncontestedly the gas of choice; furthermore, precision apparatus, in which the discharge of gas and the rate of flow are

accurately measured, is now widely available. Moreover, I have found no ill effect in several hundred patients in doing insufflation at the premenstrual phase of the cycle, followed a few moments later by endometrial biopsy. I have also insufflated a few patients during menstruation; but would be very unwilling to do either of these procedures with air. In fact, it is now my routine practice to perform insufflation in the premenstrual stage, and then do an endometrial biopsy in order to get, at one sitting, the three observations—patency, premenstrual changes, and unsuspected tuberculosis.

It cannot be too strongly stressed that a simple diagnostic procedure such as tubal insufflation must carry the minimal risk of ill effect, such as introduction or spread of infection, and that embolic death due to the test is a catastrophe that must never happen. I have tried to show that the risk of utero-tubal insufflation with air (or oxygen) is not negligible, and its use can no longer be justified. The first lesson may thus be briefly stated—carbon dioxide is unquestionably the gas of choice, and its risks are trivial.

Criteria of Tubal Blockage

The second lesson that I have learned concerns the criterion or criteria, on insufflation grounds only, of tubal blockage. For many years it has been widely accepted that a "negative insufflation" means that gas fails to pass at 200 mm. Hg (the usual upper limit) and that this implies tubal blockage. In the course of numerous tests, using 250 mm. Hg as the upper limit, I have often found that gas has passed between the 200 and 250 mm. limits. I have not encountered any ill effects or sequelae since adopting as a routine the pressure of 250 mm. Hg as the upper limit. Moreover, insufflation experiments using high pressures have been conducted in the course of abdominal operations for tubal sterilization or salpingostomy. In two cases of tubal blockage (tuberculous) a sustained pressure of 250 mm. Hg made no apparent impression on the tubes, and in another similar case the finding was the same with a pressure of 320 mm. Hg. There can be little doubt that a pressure of 250 mm. Hg is safe and that greater accuracy of results would be obtained if the routine upper limit of pressure were raised to this figure. But a single finding of apparent non-patency, even at 250 mm. Hg, is not necessarily indicative of tubal occlusion. This has been proved by the subsequent occurrence of a characteristic kymographic tracing of patency (corroborated by the demonstration of pneumoperitoneum or, in the non-anaesthetized, by shoulder pain), or by hysterosalpingography, or by the occurrence of pregnancy.

In a consecutive series of 102 patients in whom the tubes were not permeable to gas on insufflation under anaesthesia, and in whom dilatation of the cervix and endometrial biopsy were thereupon performed, repetition of the test a few days later without anaesthesia showed normal patency in 70 (69%). This would indicate that only 31% of these cases showing non-patency on a single test actually have occluded tubes. A similar finding is obtained in the anaesthetized patient if, after a negative result, the cervix is dilated to permit the introduction of a Bonney intrauterine cannula and a second insufflation is then done. Some investigators report that after one negative test they repeat it, having previously administered a sedative or an antispasmodic. They then attribute any successes to the drug. Marsálek and Zenisek (1952), however, conducted trials in 73 cases with various spasmolytic drugs (atropine, papaverine, novopon, morphine, contraspan, nitroglycerin) given before tubal insufflation, and concluded that these drugs increased muscular tone and amplitude—that is, had an effect rather opposite to spasmolysis. Admittedly, tubal spasm seems to be a frequent cause of fallacious negative findings; indeed, the purpose of cervical dilatation in these cases is to resolve this spasm.

On the other hand, as stated above, I have seen many tubes apparently non-patent under reasonably deep anaesthesia that later proved permeable to gas without premedi-

cation. The lesson is therefore that an insufflation finding of non-patency at 200 mm. Hg does not necessarily connote tubal occlusion, and that two or more tests, with the pressure advanced to 250 mm. Hg if necessary, are more likely to provide a reliable diagnosis. In the event of a negative finding in an anaesthetized patient, the cervix should be dilated and insufflation again performed. Great care should be taken before concluding that tubes are non-patent: this may be apparent and not real. If the first negative finding is obtained under anaesthesia, a second test should be performed without anaesthesia. In all cases diagnosed as non-patent, a hysterosalpingogram should be made. This is unlikely to correct the diagnosis but will provide a strong corroboration of non-patency and will usually help to demonstrate the site of occlusion.

Therapeutic Possibilities of Insufflation

The third lesson concerns the therapeutic possibilities of insufflation which have often been stressed. Many observers have recorded pregnancies following very soon after the test. The possibility, however, of chance or coincidence cannot be dismissed, and precise statistical assessment of results would be difficult. Other procedures possessing the common factor of instrumentation of the cervical canal, such as dilatation of the cervix (first advocated by MacIntosh, of Edinburgh, in 1826) and hysterosalpingography, have been known for many years to be followed frequently by pregnancy. The *modus operandi* of cure by insufflation has been discussed at length by Rubin, (1947), who believes it to be due to one or more of the following effects: (1) establishing patency of the genital tract; (2) removal of the cervical mucous plug; (3) dilatation of the tubes; and (4) possible psychic effect.

In an attempt to assess the "cervical-instrumentation factor," some six years ago I began a study of a consecutive unselected series of infertile women, in whom nothing more was done than the mere passing of a uterine sound. Three hundred patients were so treated and followed up. Of 253 patients traced, 45 (17.7%) became pregnant within 12 months after the sound was passed. This "sound" group warrants comparison with an insufflation series (Sharman, 1950), on the grounds of being unselected and of being statistically similar in respect of age distribution and duration of marriage. In the insufflation series of 902 patients with primary sterility, 271 (30%) became pregnant within 12 months. In my experience, therefore, the therapeutic effect of insufflation is much greater than that of the passing of a uterine sound. Rubin (1953) summarized the situation recently in declaring that the value of insufflation in tubal occlusion encountered in hydrosalpinx, or clubbed fimbrial ends, or atresia of the tubal lumen is purely diagnostic, but that, after subjecting data to the strictest criteria, it seems justifiable to conclude that the procedure exerts a therapeutic effect in sterile women whose Fallopian tubes obstruct the ovum.

The Kymograph as an Adjunct

The fourth lesson concerns the value of the addition of a kymograph to insufflation apparatus. In my opinion it is a valuable adjunct, and anyone who once uses it is reluctant to abandon it. The value of the kymograph is that it serves to distinguish not only between patent and non-patent tubes but also between tubes which are normally patent and those which are the site of spasm, stenosis, or peritubal adhesions. It is more accurate than the older types of insufflation apparatus, it gives a permanent record of the tests and their results, and it enables the results of tests on different dates to be compared. As a mere vehicle for passing gas into the tubes it has few, if any, advantages over the older types of apparatus; but in so far as it allows more accurate diagnosis it promotes rational treatment.

It may be asked whether the extra information gained by kymographic methods is worth the inevitable elaboration of the apparatus and the slightly increased trouble to the investigator. The reply to this is: modern apparatus has more than compensated for being elaborate by being simple

to operate. No great difference, either in the level at which patency is established or in the appearance of tubal-contraction waves, is usually seen when insufflation is repeated even after several months. Rubin (1939) maintains that the tracings can be correlated with phases of endometrial or ovarian activity. I have not been able to confirm this. More active or more frequent peristalsis may be seen at various stages of the menstrual cycle and spasm may also be exhibited for no apparent reason. Moreover, if two or three insufflations are performed on the one day—that is, within a few hours of one another—the tracings obtained need not be closely similar.

Summary

Some of the more important lessons gained from just over 4,000 utero-tubal insufflations during the past 25 years are:

(1) Practice bears out the theoretical advantages of carbon dioxide. There were only five cases of infection and no deaths.

(2) Two or more tests, with the pressure advanced to 250 mm. Hg, one at least without anaesthesia, provide a reliable diagnosis of non-patency.

(3) Primary sterility patients numbering 902 were traced for 12 months; 30% became pregnant. In a group of 253 patients in whom a uterine sound was passed, only 17.7% became pregnant within twelve months.

(4) The kymograph is a useful adjunct.

BIBLIOGRAPHY

- Bonney, V. (1924). *Lancet*, 2, 1062.
 Dible, J. H., Hewer, T. F., Ross, A. O. F., and Walsh, C. H. (1938). *Ibid.*, 1, 313.
 Faulkner, R. L. (1946). *Ohio St. med. J.*, 42, 154.
 Feiner, D. (1942). *Amer. J. Obstet. Gynec.*, 43, 639.
 Finn, W. F. (1945). *Amer. J. Surg.*, 68, 100.
 Frommolt, G. (1925). *Münch. med. Wschr.*, 72, 201.
 Furniss, H. D. (1921). *Surg. Gynec. Obstet.*, 33, 567.
 Jacoby, A. (1923). *Ibid.*, 36, 371.
 Jung, L., and Pierre, M. (1935). *C.R. Soc. Biol. Paris*, 120, 1002.
 Lenggenhager, K. (1936). *Münch. med. Wschr.*, 83, 1099.
 Mansfeld, O. P., and Dudits, A. (1934). *Zbl. Gynäk.*, 58, 2117.
 Marsálek, J., and Zenisek, L. (1952). *Lék. Listy*, 7, 419.
 Moench, G. L. (1927). *J. Amer. med. Ass.*, 89, 522.
 Richardson, H. F., Coles, B. C., and Hall, G. E. (1937). *Canad. med. Ass. J.*, 36, 584.
 Rubin, I. C. (1939). *Amer. J. Obstet. Gynec.*, 37, 394.
 — (1947). *Utero-tubal Insufflation*. Mosby, St. Louis.
 — (1953). *Lancet*, 1, 1199.
 Sharman, A. (1950). *Glasg. med. J.*, 31, 455.
 Weitzman, C., and Cohen, M. (1937). *N.Y. St. J. Med.*, 37, 1582.
 Wright, Samson (1945). *Applied Physiology*. Oxford Univ. Press, London.

"Arterial Grafting" was the subject of a meeting of the Section of Surgery of the Manchester Medical Society at which Professor C. G. Rob spoke on December 12, 1953. He began by outlining the history of the subject. In 1912 Carrel had been awarded the Nobel Prize for his researches on blood vessel grafting and the transplantation of tissues and organs; in 1913 Lexer reported that he had resected three aneurysms of peripheral arteries and restored continuity with an autogenous vein graft. The first successful arterial graft in man was inserted by Gross in 1947; he established an artery bank based on the principles elaborated by Carrel. The indications for blood vessel grafting included congenital abnormalities, such as certain coarctations of the aorta, some aneurysms and arterio-venous fistulae, wounds, primary thromboses, after some emboli, occasionally in malignant disease, and in arteriosclerosis after very careful selection. Most of these indications were obvious, but the question of arterial grafting in patients with arteriosclerotic occlusion of major vessels was debatable. These patients had a general disease; the arteriogram often showed a lesion anatomically suitable for grafting, but one was treating a patient and not an arteriogram. In all Professor Rob had grafted 35 arteries, but had treated in this way less than 3% of patients with arteriosclerosis who presented with the complaint of intermittent claudication.

DIAGNOSIS AND TREATMENT OF GALACTOSAEMIA

BY

F. PIERCE HUDSON, M.R.C.P.Ed., D.C.H.

Paediatrician

J. T. IRELAND, B.Sc., A.R.I.C.

Biochemist

B. G. OCKENDEN, M.B., B.S.

Pathologist

AND

R. H. WHITE-JONES, M.D., M.R.C.P., D.C.H.

Paediatrician

(From the Alder Hey Children's Hospital, Whiston County Hospital, and the Department of Child Health, University of Liverpool)

Galactose, formed during the metabolism of lactose, is normally converted into glycogen in the liver. In the condition known as galactosaemia this process is defective, resulting in a high concentration of galactose in the blood and its excretion in the urine. It is probable that galactose in such concentrations is toxic to some tissues and is itself responsible for the main pathological changes, but the exact pathogenesis is still uncertain. This disease is of more than academic interest because prompt treatment may bring excellent results. The original clinical description was by von Reuss (1908). Göppert (1917) was the first to report a familial incidence. Articles on the subject have appeared with increasing frequency in the past seven years, mainly in American paediatric journals. Gorter (1951) gave an account of the disease at a meeting of the British Paediatric Association, but no cases were reported in this country until Bray, Isaac, and Watkins (1952) published three and gave a full review of the literature. We know of other cases that have been diagnosed in this country, but we feel sure that knowledge of the disease is not yet widespread enough. An increased awareness will lead to earlier and more frequent detection of the disease.

The earliest signs appear in the neonatal period. The infant is reluctant to feed, may vomit occasionally, and is slow to gain weight. Jaundice is common but varies in intensity. In the most severe cases deep jaundice and ascites develop in 4 to 5 weeks and the infant dies from hepatic failure. In milder cases the infants pass gradually into a state of marasmus, and at 6 months may be only a few ounces over their birth weight. Enlargement of the liver is a constant physical finding, the edge being firm and extending nearly to the umbilicus. The spleen may be palpable. Lamellar cataracts are often found, but are not easy to detect in the early stages. Mental retardation is usually obvious by the end of the first year. Early routine investigations should reveal albumin and a reducing substance in the urine. The latter must be identified as galactose to establish the diagnosis.

Basically the treatment consists in removing lactose from the diet. When this is done rapid improvement may follow. The appetite returns, the weight increases, and the liver edge gradually recedes. Galactose disappears from the urine in one to two days and albumin a few days later. Cataracts may disappear in cases in which treatment is started early, in others needling may be necessary. Mental impairment has persisted in many