

JAUNDICE OCCURRING AMONGST BRITISH SOLDIERS ON THE RHINE, WHO HAD RECEIVED TREATMENT WITH ARSENOBENZOL COMPOUNDS.

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THE figures given in this article have been compiled from patients on the Syphilis Register at No. 25 General Hospital, Cologne, for the thirteen-month period from January, 1922, up to January, 1923, both months inclusive.

Since the autumn of 1920, jaundice following treatment with "914" and mercury has been more or less prevalent amongst the British Garrison on the Rhine, and Todd reports on fifty-three such cases which occurred during the period, March, 1920 to July, 1921, amongst British troops stationed in Cologne. These fifty-three cases occurred amongst 660 patients undergoing treatment for syphilis.

During the last few years much controversy has centred round this disease, which appears to be on the increase. Although in the majority of such cases the attack is mild it sometimes goes on to acute yellow atrophy of the liver with rapidly fatal results, therefore I think it may not be amiss to publish the following article on this most interesting subject.

Before doing so it would perhaps be better to point out that in this series of thirty-five cases some developed jaundice within a few days after receiving an injection of "914" and mercury (early benign cases). Others developed the attack after a much longer interval following their last injection. The question may well be asked, Are all these cases true toxic jaundice ones following on and caused by the administration of arsenobenzol in syphilis patients? This is difficult to answer. Widal's hæmo-clasic reaction gave a persistent positive result in those cases where it was performed, but owing to pressure of work and the time expended on this test it was only done in a limited number of cases. This would suggest that the disease was not ordinary catarrhal jaundice. Again the jaundice in this series of cases was severe and more marked than is usually the case in the ordinary catarrhal condition, the average duration of stay in hospital for each case being 55.74 days. Literature on toxic jaundice following administration of arsenobenzol compounds suggests that the interval between the last injection and the onset of jaundice can run into months. For instance Silbergleit and Fockler report upon eight cases of jaundice occurring some thirty-eight to 103 days after the last injection of the arsenobenzol compound. They also report upon thirteen cases of "acute yellow atrophy" all occurring several weeks after the cessation of treatment.

Herxheimer reports upon six fatal cases of acute yellow atrophy of

liver occurring in patients 3 to 8 weeks after the last injection of an arsenobenzol compound. Again during the Great War several cases of poisoning by trinitrotoluene were recorded in which the jaundice, one of the most prominent symptoms, occurred many months after all work with trinitrotoluene had ceased. Although I am of opinion that the jaundice in these thirty-five cases of syphilis was not an ordinary catarrhal condition, it is difficult to say what the actual cause was. I am of the opinion that the drug in use is not the sole cause, but that there appears to be some other causative agent acting on a liver already deranged owing to treatment with the arsenobenzol compounds, perhaps bacterial infection.

During the period in question, 768 men were on the Syphilis Register either under observation for syphilis, or receiving treatment for this disease.

Of this total thirty-five suffered from jaundice at a short or a long interval following the administration of "914" and mercury. This gives a percentage of 4.55, a higher percentage than is usually recorded in this disease. The Medical Research Council in their Special Report Series, No. 44 of 1915, give a percentage of 0.56 taken from 39,377 cases of syphilis.

The above percentage figure, 4.55, actually refers to cases of jaundice occurring amongst these 768 syphilis patients whilst they were stationed on the Rhine, and within this given period of thirteen months.

The Mayo Clinic in America give a percentage of 1.3 taken from 5,200 syphilis patients.

Jaundice in syphilis patients, however, appears to be more prevalent and more apt to occur amongst British troops on the Rhine than amongst our troops in Home Garrisons. The reason why this should be so is difficult to explain. During the period in question, there were in addition ninety cases of catarrhal jaundice unconnected with the administration of arsenobenzol compounds. The average monthly strength of the British Garrison for this period was approximately 6,578.

Jaundice appears to be prevalent in Germany and is stated to be more prevalent in Northern Germany than in the South. The average duration of stay in hospital for these thirty-five cases treated for jaundice works out at 55.74 days each.

Table "A" shows stage of syphilis on commencement of treatment when patient was first placed on the Syphilis Register, the quantity of "914" and mercury administered in each case prior to the onset of jaundice and the interval between the last dose of "914" and admission to hospital for this complaint.

In all cases the dosage of "914" is given in grammes administered intravenously and that of mercury in grains administered intramuscularly, the latter drug being given in the form of mercurial cream.

Of these 35 cases, 18 received neokharsivan without any other arsenical preparation, 13 received both neokharsivan and novarsenobillon, whilst the remaining 4 received novarsenobillon only. All these cases received mercurial cream in addition as can be seen by reference to Table "A."

During this thirteen months period, 284 injections of neosalvarsan with mercury were given and no jaundice occurred following the administration of this arsenobenzol compound.

Of the thirty-five cases, thirty-one received neokharsivan either alone or with novarsenobillon. Neokharsivan has not been in use at No. 25 General Hospital since July, 1922.

TABLE "A."—TABLE SHOWING STAGE OF DISEASE (SYPHILIS) ON COMMENCEMENT OF TREATMENT, QUANTITY OF "914" AND MERCURY GIVEN PRIOR TO ONSET OF JAUNDICE, AND INTERVAL BETWEEN LAST INJECTION OF "914" AND ADMISSION TO HOSPITAL FOR JAUNDICE:

Serial No. in Syphilis Register	Stage of syphilis when treatment commenced	Total quantity of "914" and Hg administered prior to onset of jaundice	Interval between last injection of "914" and admission to hospital for jaundice
795	Late primary	NK 3.75 grm., Hg 6 gr.	78 days
823	Early primary	NK 4.20 grm., Hg 5 gr.	8 "
822	Late primary	NK 3.75 grm., Hg 7 gr.	60 "
834	Early primary	NK 3.75 grm., Hg 6 gr.	40 "
824	" "	NK 3.75 grm., Hg 7 gr.	85 "
687	Late primary	NK 7.05 grm., Hg 12 gr.	95 "
887	Early primary	NK 2.55 grm., Hg 5 gr.	37 "
832	Late primary	NK 6.30 grm., Hg 11 gr.	7 "
875	" "	NK 3.15 grm., Hg 4 gr.	89 "
986	Early primary	NK 3.75 grm., Hg 7 gr.	157 "
910	Late primary	NK 3.75 grm., Hg 7 gr.	98 "
972	" "	NK 3.75 grm., Hg 7 gr.	69 "
964	" "	NK 3.75 grm., Hg 3 gr.	68 "
1,074	" "	NK 1.35 grm., NAB 1.20 grm., Hg 5 gr. ..	14 "
872	" "	NK 3.75 grm., Hg 7 gr.	43 "
956	" "	NK 3.75 grm., Hg 7 gr.	101 "
965	" "	NK 3.75 grm., NAB 1.35 grm., Hg 10 gr. ..	5 "
1,021	Early primary	NK 3.75 grm., NAB 0.90 grm., Hg 7 gr. ..	33 "
1,104a	Late primary	NAB 3.75 grm., Hg 7 gr.	7 "
977	Early secondary	NK 2.55 grm., Hg 4 gr.	140 "
1,043	Early primary	NK 3.75 grm., NAB 0.90 grm., Hg 7 gr. ..	40 "
1,050	Late primary	NK 1.35 grm., NAB 1.20 grm., Hg 5 gr. ..	76 "
1,038	" "	NK 3.15 grm., NAB 1.05 grm., Hg 8 gr. ..	1 day
994	" "	NK 3.75 grm., Hg 7 gr.	118 days
1,031	" "	NK 3.75 grm., NAB 0.90 grm., Hg 9 gr. ..	5 "
1,032	Early primary	NK 3.15 grm., NAB 1.50 grm., Hg 7 gr. ..	48 "
1,037	Late primary	NK 3.75 grm., NAB 0.45 grm., Hg 8 gr. ..	22 "
1,055a	Early primary	NK 1.35 grm., NAB 3.30 grm., Hg 6 gr. ..	27 "
1,058	" "	NK 3.15 grm., NAB 1.50 grm., Hg 7 gr. ..	85 "
917	" "	NK 4.65 grm., Hg 7 gr.	164 "
996	" "	NK 1.35 grm., NAB 3.30 grm., Hg 6 gr. ..	44 "
1,010	" "	NK 3.75 grm., NAB 0.90 grm., Hg 7 gr. ..	125 "
1,161	Late primary	NAB 3.75 grm., Hg 7 gr.	64 "
1,144	" "	NAB 3.75 grm., Hg 7 gr.	72 "
1,200	" "	NAB 3.75 grm., Hg 7 gr.	117 "

Of the 35 cases alluded to, 13 were in the early primary stage with a negative Wassermann blood throughout, 21 were in the late primary stage and only 1 in the early secondary stage. This would tend to demonstrate that syphilis in itself is not the cause of jaundice, for if so then one would expect to see a larger proportion of cases occurring amongst the later syphilides, such as florid secondaries, where the toxins of syphilis are more abundant and widespread throughout the tissues of the body. An

additional proof that syphilis itself is not the cause lies in the fact that of the 35 cases recorded herein, 29 gave a negative Wassermann reaction at the test last done prior to onset of jaundice, 3 gave a strong positive reaction, 1 was positive and 2 partially positive. Again, jaundice in syphilis cases prior to treatment with arsenobenzol does not appear to be as frequent as in recent years. Werner, in 1899, gives the percentage as 0.37 amongst 15,799 cases of syphilis; of course these never had arseno-benzol treatment.

The jaundice does not appear to be due to an overdose of arsenic. By scrutinizing Table "A" it will be seen that in Serial Nos. 887, 1,074, 977 and 1,050, jaundice occurred after the administration intravenously of 2.55 grammes of "914" in each case, these injections being spread out over periods of 75, 40, 42 and 43 days respectively; not large doses for this organic preparation of arsenic. Just recently I have seen a case of syphilis develop an acute attack of jaundice after receiving two intravenous injections of novarsenobillon consisting of 0.45 gramme each, with one week's interval between the two. There are also other cases on record to show that the disease may appear after a small total dosage of 0.90 gramme of an arsenobenzol compound given to a syphilis patient.

Again if the disease is entirely due to the arsenobenzol compound then it would appear to be dangerous to repeat the drug at a short interval after recovery. I have not found any danger in doing so. In fact in several cases treatment with "914" and mercury was recommenced within a few days after the patient was discharged hospital for jaundice. For instance, Serial Nos. 795 and 834 commenced treatment again two days after discharge from No. 3 General Hospital, having suffered from jaundice. Serial No. 1031 recommenced treatment within seven days after discharge from hospital and went straight through with a 5/6 course (5/6 equals: 5 injections of "914" and 6 injections of mercury with weekly intervals). Serial Nos. 687, 1,074 and 872 started treatment 21, 20 and 12 days after discharge from hospital for jaundice and went straight through 6/7, 5/3 and 6/7 courses respectively without the slightest trace of the recurrence of their jaundice and without any untoward result.

Surely this is evidence to show that the drug is not the sole cause of jaundice in syphilis patients. Herxheimer and Milian find no danger in giving further treatment with arsenobenzol after this disease. Again, jaundice does not appear to be due to cumulative action on the part of the arsenobenzol compound in use, as the disease has been shown to occur after a very small dose—0.90 gramme of "914." Again, if due to cumulative action, then the disease ought to be more frequent in cases receiving the arsenobenzol compound intramuscularly than when administered intravenously, as in the former method arsenic appears to be excreted more slowly from the system; however jaundice appears to occur just as frequently when "914" is given by the intravenous route. It may be that this obscure form of jaundice is not due to any one source but caused by several factors all acting in unison, the chief of these being (1)

Syphilis, (2) Treatment with arsenobenzol compounds; (3) Personal susceptibility on the part of the patient, and, perhaps in addition, (4) Bacterial infection, which travels up from the intestines in the form of an ascending cholangitis. Some years ago when stationed in Wellington, Southern India, I was much impressed by the number of paratyphoid patients returning from active service, in Mesopotamia with jaundice as a complication, cases in which there was no history of syphilis. Alcohol may be a predisposing factor in the causation of these jaundice cases, as alcohol in itself has action on the liver cells, and then arsenobenzol compounds containing arsenic may overcome a weak-resisting liver causing insufficiency of the hepatic cells, etc., and jaundice. On the Rhine where this jaundice is prevalent alcohol is cheap and freely indulged in by the British soldier in the form of beer and a special decoction called "green light," a mixture of several ingredients much fancied by our troops. Against the theory of alcohol being a predisposing cause is the fact that of this series of thirty-five cases no fewer than seven were total abstainers. Amongst this series of cases ten, or 28.57 per cent, had, previous to the onset of jaundice, received intramine intramuscularly; this suggests that intramine is not a preventive as laid down in some books.

The cases occurring on the Rhine were spread over a wide area, and not confined to any separate unit nor to any special barracks. The disease did not arise in any special batch number of the arsenobenzol compound, and therefore does not appear to be due to toxicity on the part of the drug.

The danger signal of a commencing erythema in a sensitive patient was not seen in the thirty-five cases dealt with in this article, although this physical sign was carefully watched for. Eczema of the scrotum and legs however did occur in one of these patients. Stomatitis was present in seven cases, or twenty per cent. In my opinion stomatitis is not necessarily a precursory warning of following jaundice, in fact stomatitis is apt to occur in all cases receiving mercury, especially where the teeth are carious and in those patients who do not attend to the hygiene of their mouths. It is, however, a symptom not to be entirely ignored. Preliminary symptoms are often conspicuous by their absence, some patients not knowing they were jaundiced until told by a comrade; others have certain physical signs and symptoms, the most common of which are:—

- (1) A gradual loss of weight.
- (2) Malaise and loss of appetite.
- (3) Nausea; frequently this occurs without vomiting, and comes on independently of the taking of food, often in the morning before breakfast.
- (4) Tenderness over the epigastric area.
- (5) Anæmia.
- (6) Dislike for fatty foods.

These symptoms occur early before the sclera turn yellow. With reference to the loss of weight the usual thing is for the patient to put on weight when treatment is commenced, then this stops and patient

gradually commences to drop a little weight weekly. This was marked in several of the cases in Table "A."

In twenty-eight cases no stomatitis was present up to onset of the jaundice. In seven cases stomatitis was present but not severe.

Widal's hæmoclasic reaction (leucocyte count before and after a meal) appears to be an important test to discriminate between this disease and ordinary catarrhal jaundice, when it gives a persistent positive reaction as tested on more than one occasion before and after a meal. Prognosis in the majority of cases is good, especially in early benign cases. The attack is more severe in late cases, and is very grave in those cases developing acute yellow atrophy of the liver. Serial No. 1,161 is an example of this latter condition, and this case is fully reported upon at the end of this article. Prognosis is good in those cases which lie up early and receive proper diet and treatment. Intestinal hæmorrhage is a grave sign and generally seen in those fatal jaundice cases with acute yellow atrophy of the liver.

Treatment.—Rest in bed. Carbohydrate diet without fats and with very little proteid. Glucose internally and large doses of sodium bicarbonate, as well as mild laxatives. A general anæsthetic should not be given in such cases. If chloroform has to be given for any reason glucose should be given before and after administration of the anæsthetic.

There is one type of jaundice where a diagnosis of scarlet fever is apt to be made, namely in those acute cases coming on quickly a few days after an injection of "914." Patient suddenly becomes ill with headache, vomiting and fever, then a couple of days later out comes a profuse small papular scarlatiniform rash all over the body resembling the boiled lobster appearance of scarlet fever, but without the strawberry tongue and without the circumoral pallor; such cases have been erroneously diagnosed as scarlatina. These cases within a few days show all the signs of jaundice, which confirms the diagnosis.

By kind permission of the Officer Commanding No. 3 General Hospital and of Captain A. S. Blackwell, Royal Army Medical Corps, I am allowed to publish notes and post-mortem result on one fatal case of jaundice following arsenobenzol treatment at No. 3 General Hospital, Cologne, in January, 1923. This case is alluded to in this article under Serial No. 1161.

I had no chance of seeing this man during his illness in January, being on leave in England at the time.

CLINICAL NOTES AND POST-MORTEM RESULT OF SERIAL NO. 1161, WHO DIED OF JAUNDICE FOLLOWING ADMINISTRATION OF "914" AND MERCURY.

History prior to Onset of Jaundice.—The patient came under treatment for late primary syphilis (his first attack of venereal disease) on September 9, 1922. He commenced treatment on the same date and completed a

"B" course on November 15, 1922. This course consisted of 3.75 grammes of novarsenobillon and eight grains of mercury. Patient showed no intolerance to the drugs and put on weight, urine was free from albumen throughout this treatment. After his course on November 22, 1922, his blood gave a negative Wassermann reaction.

History of Fatal Attack of Jaundice.—Patient was admitted to No. 3 General Hospital on January 17, 1923. He stated that he noticed his eyes yellow for some three or four days previous to admission. Patient examined: no tenderness over epigastric area, slight nausea, spleen not enlarged. Placed on fat-free diet, with mist. rhei co. by mouth. January 21, 1923: Jaundice now more marked, occasional nausea, has vomited a few times since admission. Liver appears diminished in size. Leucocyte count fasting and after food gave a positive Widal's hæmoclasic reaction. January 25, 1923: No improvement, pulse running slow, 52 to 58 per minute. January 28, 1923: Patient's condition worse, jaundice now deeper, vomiting more persistent. Urine loaded with bile pigment, albumen and casts present. Severe pain complained of in the epigastric area. Patient taking sod. bicarb. grains 30 quartis horis. Patient on "seriously ill" list. January 29, 1923: Condition worse, still vomiting and becoming drowsy. Lies curled up in bed, resents all interference. Bowels not open to-day nor yesterday. Calomel grains 3 given. Pulse still slow, 56 to minute. The sharp lower edge of liver can be felt on inspiration, only a little urine now being passed. Patient on "dangerously ill" list. January 30, 1923: No urine passed since 15.00 hours yesterday, has not vomited during the past twenty-four hours. Semi-conscious. Skin dry and hot bottles in blankets resorted to in order to produce sweating, which had the desired effect. Pulse now quicker, 78. Twenty ounces urine drawn off with catheter. Urine contains many epithelial and granular casts. General rigidity of body. No retraction of neck, knee-jerks increased. Babinski's sign present. Abdomen rigid and apparently tender, resents being moved or touched anywhere. Pulse in the afternoon became rapid (148 per minute). Bowels constipated, enema given but no result; followed by croton oil one minim. Towards the evening Cheyne-Stokes respiration set in. Patient comatose. Pulse gradually failed. Died at 19.00 hours. Temperature never rose above normal.

Result of Post-mortem Examination carried out Seventeen Hours after Death.—Body: Fairly well nourished. Deeply jaundiced. Rigor mortis passing off. Head: Brain and membranes bile-stained. No naked-eye lesions to be seen. Chest: Left lung congested, adherent throughout to the parietal pleura and diaphragm. Visceral pleura thickened. Right lung congested, otherwise normal. Pericardium: Normal. Heart: Normal size, all valves competent, apparently healthy. Abdomen: No free fluid, numerous small petechial hæmorrhages in the mesentery of small and large intestines. A few petechiæ seen in parietal peritoneum—especially in pelvis. Stomach and intestines normal. All organs bile-stained. Liver: Small

less than half the usual size. Substance soft but not diffuent. Mottled greenish brown. Lobules clearly marked, almost like nutmeg liver. Spleen: Normal in size and consistency. Pancreas: Appears normal. Kidneys: Normal in size. Cortex pale, capsule stripped easily. Sections of liver, kidneys, pancreas and spleen were sent to the Royal Army Medical College, London, and very kindly examined by Lieutenant-Colonel Marrian Perry, R.A.M.C., Professor of Pathology, whose report on the histological changes found is as follows:—

“Sections from the various organs—liver, spleen, pancreas and kidneys, were treated by Levaditi's method for demonstration of spironemata. The result in each case established the absence of these organisms.

“*Histological Investigation.*—Kidney: The sections demonstrated considerable vascular engorgement, with, in the greatest part of the organ, areas of interstitial hæmorrhage. The chief pathological changes were noted in the epithelium lining the convoluted tubules. The epithelial cells of the tubules were very evidently affected by cloudy swelling, granular degeneration, or a mixture of both. The lumen of some of the tubules was blocked by desquamated epithelium, leucocytes, or collection of red blood-cells. The changes were such as would classify the condition as an *acute diffuse tubular nephritis*. Pancreas: No changes of any importance were evident in this viscus. The various cellular elements were clearly defined, and no indication of hæmorrhagic or other variety of pancreatitis was present. Spleen: No changes of any importance from normal were noted. Liver: The histological changes in this organ were widespread and most striking. The usual microscopic appearance of the living tissue had undergone complete metamorphosis, and but for the fact that the characteristic features of the bile ducts were evident, difficulty would have been experienced in recognizing the fact that the sections had been made from hepatic tissue. The liver lobules were completely disorganized, the majority of the cells had become completely necrotic, and were replaced by a disintegrated debris of cells. In a few scattered areas some more or less normal hepatic cells were evident, and many of these cells showed two or more nuclei. These are apparently cells which have escaped the toxic action and are evidencing signs of active proliferation. In the larger area the structure consisted of the surviving connective tissue of the organ with its blood vessels and masses of the granular debris referred to above. As has been noted the bile ducts were a prominent feature in these areas. The condition bears a close resemblance to the changes met with in sub-acute yellow atrophy or to the appearance encountered in the organ in fatal cases of infective jaundice.”

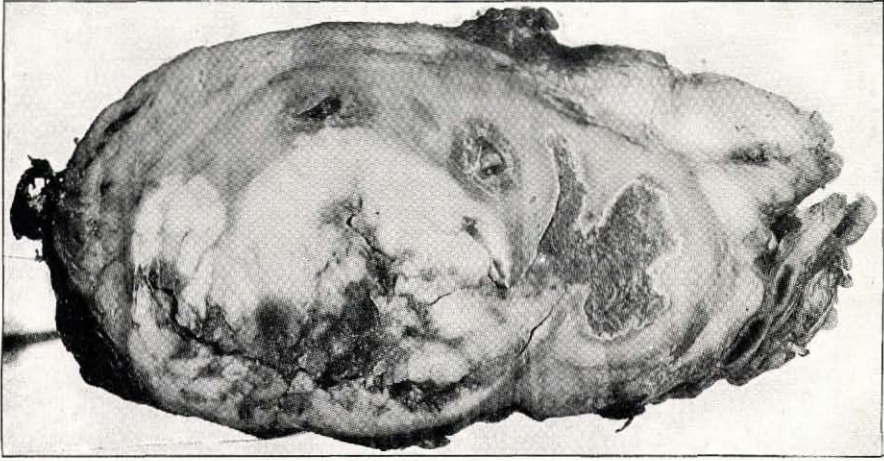


FIG. 1.

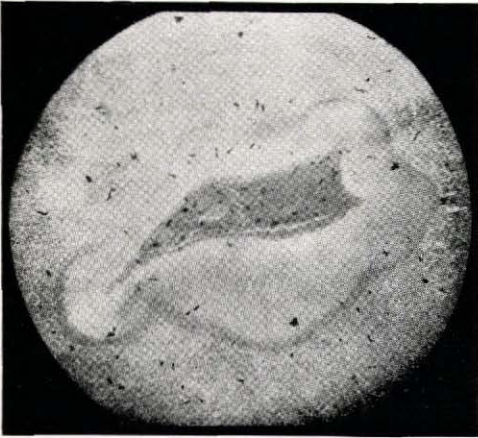


FIG. 2.

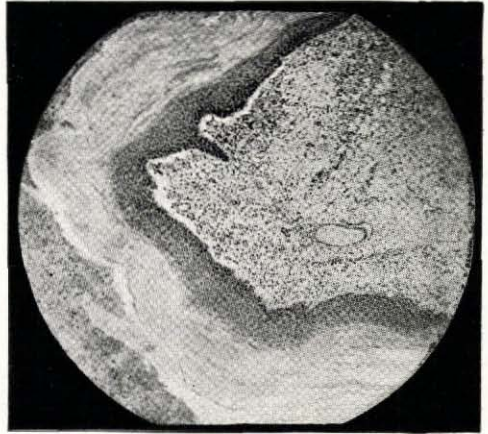


FIG. 3.



FIG. 4.

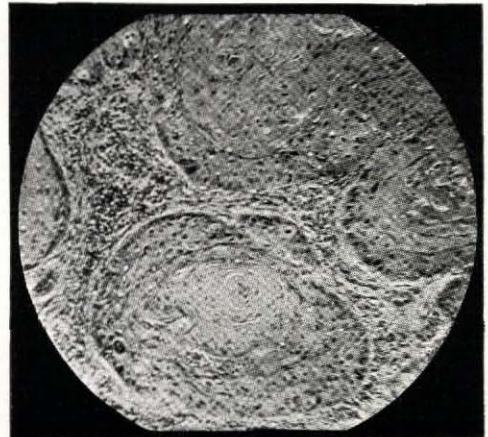


FIG. 5.

To illustrate " Epidermization of the Transitional Epithelium lining the Pelvis of the Kidney, followed by Squamous-celled Carcinoma, and other Changes," by Major J. A. MANIFOLD.