Discussion

There appears to be no significant difference between the results obtained with the treatments consisting of 6 grains of quinine daily, and of 6 grains of quinine plus 'chhatim' daily. In such small groups of cases (8 and 9 cases) differences in results would have to be very marked before they were significant. From some aspects, such as control of clinical attacks in *P. falciparum* infections, the results in the quinine group are slightly better; from others, such as parasite relapse rate, especially for *P. vivax*, and the period before a relapse with the latter species, the results are slightly better in the quinine-'chhatim' group. Only the clinical relapse rate is appreciably lower in the quinine-'chhatim' group, but the validity of this finding for comparative purposes is questionable, firstly because the groups are so small that such differences are not statistically significant and secondly because 2 out of 7 cases which had a parasite relapse could not be followed up to determine whether a clinical relapse also occurred. It will be observed that in most instances parasites could be detected a few days before the clinical relapse.

The results in the cases which relapsed after quinine treatment and were re-treated as in the quinine-'chhatim' group add nothing in favour of 'chhatim'. The preceding remarks refer mainly to *P. falciparum* and *P. vivax* infections, for too few cases of quartan malaria have been studied to draw conclusions in respect of *P. malariæ*.

A point which deserves notice is that the cases in the quinine group had comparatively heavy parasitic infections; thus 50 per cent gave counts exceeding 10,000 parasites per c.mm. as against 22 per cent in the quinine-'chhatim' group. In spite of this, the results in the latter group are not correspondingly better, suggesting that 'chhatim' exercised no appreciable synergistic action on quinine.

Summary

In view of reports that *Alstonia scholaris* ('chhatim') greatly enhances the action of quinine in the treatment of malaria, so that a comparatively small dosage of the quinine suffices to effect a cure, a study was undertaken of the synergistic action of 'chhatim'. Seventeen cases of malaria, all of several weeks' duration, were treated in two main groups: (*i*) a quinine or control group of 8 cases treated with 2 grains of quinine sulphate t.d.s. for 6 days, (*ii*) a quinine-'chhatim' or test group of 9 cases treated with 2 grains of quinine sulphate combined with 12 grains of powdered bark of *Alstonia scholaris* of known alkaloidal content t.d.s. for 6 days. The efficacy of the two treatments was studied by both clinical and parasitological methods. There was no significant difference between the results obtained in the two groups, suggesting that 'chhatim' exercises no synergistic action on quinine. It was found that 2 grains of quinine sulphate t.d.s. for 6 days controlled both fever and parasites in a large proportion of cases, but relapses after short periods were very common. There is, therefore, hardly any justification for using such small doses of quinine in the treatment of malaria. In fresh cases of malignant tertian infections particularly it would actually be unsafe to rely on this small dosage, in that one cannot judge the seriousness of the disease by examination of the peripheral blood smears alone; nor can one foretell which case will take a serious turn. Perhaps from these and other considerations, the Malaria Commission of the League of Nations (1937) suggested a dosage schedule of 5 grains t.d.s. for 5 to 7 days in the treatment of malaria.

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[*Note.*—Our experience confirms the opinions expressed in this paper. In chronic and relapsing malaria with relatively low-grade infections, the fever can often be controlled by doses of quinine as low as 6 grains a day; the addition of 'chhatim' appears to make little if any difference. With fresh infections of malaria, which are usually of much higher grade, the use of such small doses is often of little use and actually dangerous. In one case of heavy infection with *P. falciparum* seen by the editor, quinine and 'chhatim' used as described above completely failed to control the fever and the patient died. In other similar cases, the treatment had to be abandoned for a larger dose of quinine, which controlled the fever.

Even if the fever is controlled with these small doses of quinine, with or without 'chhatim', the relapse rate is so high that further courses have to be given, and ultimately there is no saving of quinine. We fear therefore that the attempt to make quinine supplies go further, by using small doses in combination with 'chhatim', are not likely to meet with much success, and moreover have certain very real dangers.

Both the above paper and that of Roy and Chatterjee deal with cases treated at the end of the malaria season, and mostly with cases of several weeks' duration with only what amounts to a residual low-grade infection. If the work had been done in the malaria season on cases of heavy fresh infection, the results of treatment would, we feel, have been very different.—EDITOR, *I. M. G.*]

MACROCYTIC ANÆMIA

THE UNKNOWN HÆMOPOIETIC FACTOR IN WHOLE LIVER AND YEAST

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CASES of macrocytic anæmia that resist parenteral liver and marmite but yield to whole liver or yeast are now reported by various

workers all over the world. As far back as 1938 Napier and his co-worker reported that macrocytic anæmias in the tropics including those of pregnancy could be grouped on therapeutic grounds as (*a*) curable with refined liver extract such as anahæmin, (*b*) curable with crude liver extracts or marmite, and (*c*) curable with campolon. We now see that a fourth group which resists even campolon but yields to whole liver or yeast is added to the list. However, the anti-anæmic substance that is missing from or not present in sufficient quantity to be active in crude and refined liver extracts, but is present in whole liver and yeast, has not yet been identified. The purpose of this communication is to produce clinical evidence to suggest the probable identity of this unknown hæmopoietic factor, and to show that, in such refractory cases, deficiency of nicotinic acid exists and at a certain stage of the illness reaches a definite degree of intensity at which the anæmia and other associated conditions defy all treatment with parenteral liver, marmite and high protein diet unless the deficiency is met by exhibition of pure nicotinic acid or its rich sources, whole liver or yeast. I give below a few illustrative cases from my records in support of my view.

Case 1.*—A man had acute diarrhœa and vomiting in 1936 which persisted in sprue-like form with severe anæmia for a year and was relieved with a course of torantil, abidol and campolon. He had a relapse in 1939. Old remedies failed and his anæmia resisted intensive therapy with campolon, betaxin and other drugs. Nicotinic acid deficiency was suspected and the additional therapy tried.

Condition of circulatory system before nicotinic acid.—R.B.C. 2.9 millions, Hb 90 per cent, C.I. 1.5, W.B.C. 5,312 and a blood picture of megalocytic hyperchromic anæmia. B.P. 92/50. Dyspnœa, rapid pulse, weak and dilated heart with bruit and swelling of whole body present. Expected to die at any moment.

After nicotinic acid therapy.—R.B.C. 3.15 millions, Hb 90 per cent, W.B.C. 13,125, size of R.B.C. normal. B.P. 110/70. Œdema disappeared, heart became normal and he began to walk about, and all in 20 days. He gained 42 lb. in 2 months. No relapse for 4 years.

The response was so rapid and complete that I could not help believing that nicotinic acid had some unknown properties to quickly regenerate the depressed hæmopoietic system.†

Case 2.—A man was admitted into our hospital in 1940 with fever, extreme degree of anæmia, dyspnœa, palpitation and troublesome indigestion. He had similar attacks in 1929, 1933 and 1939. He received 44 c.cm. of campolon with great benefit during the third attack. Resisted all injections, tonics and hæmatinics during the fourth attack. Nicotinic acid was not available. Yeast, raw liver juice and high protein diet were prescribed.

Condition before the treatment.—Macrocytic anæmia with R.B.C. 1.7 millions, Hb 45 per cent, C.I. 1.3, W.B.C. 9,000, polymorphonuclears 40 per cent, lymphocytes 58 per cent. Anisocytosis and poikilocytosis present. B.P. 90/45. No ankylostoma or any other ova in the stools. Van den Bergh negative. Achlorhydria on fasting and after porridge meal.

Condition after the treatment.—R.B.C. 3.58 millions, size of R.B.C. 7.8μ, Hb 55 per cent. Anisocytosis and poikilocytosis not present. B.P. 115/65. HCl returned in gastric juice. Clinically cured and remained so when examined after a year. No relapse now for last 3 years.

The anæmia in this case resisted liver injections but responded to liver by mouth and yeast. The response, however, was not so rapid as with nicotinic acid.

Case 3.—A female had gastro-intestinal troubles and severe anæmia starting after child-birth. She suffered for 4 years. Hundreds of iron, liver and calcium injections with other drugs were given without any effect. She became pale, weak and emaciated and then suddenly developed cramps in the legs and pain in the abdomen. She gasped for breath and appeared to be dying. Signs of intense anæmia and acute depletion of nicotinic acid were present. She was given 10 c.cm. hepatex with 50 mgm. of nicotinic acid in 20 c.cm. of 25 per cent glucose intravenously. Her abdominal pain lessened and cramps disappeared immediately. A full course of nicotinic acid with other appropriate treatment was then given.

Condition before nicotinic acid.—R.B.C. 1.2 millions, size of R.B.C. 8.5μ, Hb 22 per cent, BP 80/45. Stool showed no ova, no cyst, no ankylostoma and no characteristics of sprue. *X*-ray revealed extreme enteroptosis and no other abnormality.

Condition after nicotinic acid.—R.B.C. 3.5, size 7.5μ, Hb 75 per cent. She was able to walk about in a week and could do a mile without fatigue in a month. She became clinically normal but often had 2 to 3 stools a day after some indiscretion in food. She has remained well for 3 years.

Case 4.—Female, aged 21 years. Pseudo-pernicious anæmia of pregnancy successfully treated with parenteral liver and blood transfusions during first and second pregnancies. Third ended in an abortion and fourth in still birth after which the anæmia became refractory to parenteral liver and three blood transfusions. I gave 28 c.cm. of refined liver extract, 44 tablets of fersolate with marmite and a liberal diet. There was no response. I then gave 25 c.cm. of campolon and 18 mgm. of berin in 9 days. There was a slight improvement, R.B.C. rising from 1.2 millions to 1.5 millions. I then tried 300 mgm. of nicotinic acid intravenously given in 10 days. The response and recovery were dramatic.

Condition under refined and crude liver extracts, marmite and iron.—R.B.C. 1.2 millions, size 8.1μ, Hb 30 per cent, C.I. 1.25. Œdema of feet and eyelids. Râles and rhonchi in lungs, severe cough, extreme weakness and restlessness. Wassermann negative in husband and wife.

Condition under nicotinic acid.—R.B.C. 3.8 millions, size 7.8μ, Hb 70 per cent, C.I. 0.9. She became normal but took liver soup and nicotinic acid tablets as maintenance treatment for 6 months. She has been well for 3 years.

Case 5.—A male, aged 24 years, had gastric pain, tender sigmoid and severe anæmia for 6 months. He became bed-ridden and was admitted into a railway hospital on 23rd October, 1940.

No history of dysentery; no ova or cyst in the stool; no albumin or sugar in urine; he was given a course of emetine, santonin, liver extract intramuscularly and iron, arsenic and nux vomica mixture and a milk and sago diet for 20 days by my colleague. There was no relief. His stool was again examined on 4 successive days but no ova, cyst or ankylostoma found. He was then given 2 c.cm. of hepatex injection daily and 30 grains of ferri et ammoni citras and 1 drachm of dilute HCl 3 times a day with suitable diet for 10 days which gave no relief whatsoever.

I then took the patient in hand. He gave a history of dyspepsia for 6 years. Constipation, tympanitis and epigastric pain gradually getting worse, nausea and vomiting in the morning and, later, during the day for a few months. Patient was very weak, pale and anæmic and positively 'mental' with disturbed dreams. Knee jerks absent. Lungs normal. B.P. 84/40, R.B.C. 1.8 millions, size 8.4μ, Hb 40 per cent, C.I. 1.1. Nothing

*Details of case 1 will be found in *J. I. M. A.*, **12**, 1, and of others in *Patna Journ. Med.*, **17**, 1.

†In this case the anæmia apparently persisted but did not remain megalocytic.—EDITOR, *I. M. G.*

in stool and urine. Weight 76¾ pounds. Achlorhydria on fasting and after porridge meal. Nicotinic acid intravenously was intentionally not given to see the effect of parenteral liver extract plus marmite and high protein diet. He was given 4 c.cm. of hepatex intramuscularly on alternate days and a liberal diet with marmite plus one drachm of dilute HCl and ½ drachm of ferri et ammon. cit. 3 times a day for 10 days, with the result that his R.B.C. went down from 1.8 millions to 1.6 millions, his weight did not increase but his Hb rose from 40 to 60 per cent. I then ordered 10 c.cm. campolon first day and 5 c.cm. on third, fifth and eighth day with 2 mgm. of berin intramuscularly every day. Iron and HCl remained the same. Pepsin was given after meals. His diet was 1 cup of orange-juice at 6 a.m., 2 lightly boiled eggs, 2 biscuits, 1 cup of milk with ovaltine and marmite at 8 a.m., vegetable or meat soup, minced chicken, light pudding, marmite and fruit-juice at 12 a.m. A cup of milk with ovaltine if required at 4 p.m. and a soup, a meat or fish dish, marmite and pudding at 8-30 p.m. His Arneth count pointed to a septic focus for which a sulphonamide intramuscularly was tried. After 2 weeks of this intensive dietetic, medicinal and parenteral liver therapy the result was swelling of his feet and face. His urine was still normal. After 3 weeks his R.B.C. was 1.6 millions, size 8.2μ, Hb 50 per cent, W.B.C. 3,120, polymorphonuclears 80 per cent, lymphocytes 18 per cent, monocytes nil, eosinophils 2 per cent, poikilocytosis present, œdema of feet, legs and face increased, vomiting very troublesome. Positive signs of nicotinic acid deficiency appeared. Weight not increased.

All medicines were then stopped to see the effect of nicotinic acid therapy; the diet continued to be the same. Fifty mgm. of nicotinic acid in 25 c.cm. of 25 per cent glucose intravenously on alternate days and then every fourth day up to sixth injection was given. The response was rapid. His blood on 28th December, 1940, showed R.B.C. 2.6 millions, Hb 70 per cent, size of R.B.C. 7.8μ, W.B.C. 8,426, polymorphonuclears 71 per cent, lymphocytes 24 per cent, eosinophils 5 per cent. He was given 10 injections in a month. Œdema disappeared. HCl after porridge meal returned. Discharged to duty on 17th January, 1941, as much improved. His blood on 31st March, 1941, was R.B.C. 3.22 millions, size 7.0μ, Hb 55 per cent, B.P. 95/55, weight 78½ pounds. His weight after 6 months was 81¾ pounds, and blood almost normal. His weight after a year was found 93½ pounds and blood normal. He still takes a cup of liver soup twice a week and has been well for 3 years.

Comment.—The anæmia resisted parenteral liver during the second and fourth attack in cases 1, 2 and 4 and in the late stages of the first attack in cases 3 and 5 when signs suggestive of secondary pellagra could be detected in case 1 and of a pre-pellagrous condition in cases 2 and 4 and very faint suggestions of deficiency in cases 3 and 5. These facts suggest that the resistance to parenteral liver developed only when nicotinic acid deficiency reached a definite degree of intensity.

A careful study of the clinical features of other workers' cases also shows probable signs of nicotinic acid deficiency. In Bagchi's 94 cases (1943) 27.5 per cent had diarrhœa and 10 per cent had soreness of the mouth. Of the three cases of Fullerton (1943) one had burning pain in the tongue and superficial ulcer on its each margin and the second had diarrhœa and pain in the tongue and even atrophy of tongue papillæ. Thirty-three per cent of Taylor and Manchanda's cases (1940) had soreness of the tongue and 25 per cent had actual glossitis.

Case 5 effectively demonstrated that nicotinic acid gave a rapid hæmopoietic response independently of whole liver and yeast when parenteral liver, marmite and high protein diet totally failed. I have no doubt that these cases would have been taken to have marrow aplasia and if nicotinic acid in some form or other was not given to them they would have proved fatal.

Discussion.—According to Castle's theory, macrocytic anæmias are caused by (*a*) deficiency of extrinsic factor in the food, (*b*) permanent or temporary failure of secretion of intrinsic factor in the stomach, (*c*) deficiency of both the factors, (*d*) interference with the combination or absorption of the hæmopoietic principle formed by both the extrinsic and intrinsic factors. Liver was first found to give marvellous results in true Addisonian and other macrocytic anæmias. Castle's extrinsic factor was then available in the form of marmite and nutritional anæmias like 'tropical macrocytic anæmia' yielded to it favourably. McRobert, Reddy and Subramanian (1940) reviewing 100 cases of anæmia admitted into the General Hospital, Madras, found 7 cases of macrocytic type, 6 of which were achlorhydric. They all yielded to marmite. Napier (1936) and others also reported good results with marmite in such cases. It has thus been commonly believed that macrocytic anæmias respond favourably to adequate parenteral liver and marmite, and that a case not responding to intensive and extensive therapy of such a kind is supposed to have marrow hypoplasia, and to show a grave prognosis. This outlook has been responsible for a very high mortality specially amongst the cases of severe type of macrocytic anæmia of pregnancy. Bagchi (1943) giving an analysis of 107 cases of anæmias in pregnancy treated in the Carmichael Medical College Hospitals, Calcutta, noted that in as many as 104 cases, the anæmia could not be attributed to any cause outside pregnancy, and that 94 of them belonged to hyperchromic-orthochromic varieties of tropical macrocytic and pseudo-pernicious anæmia of pregnancy. The treatment given was intensive iron and parenteral liver therapy with intramuscular injection of whole blood, plus a liberal diet and blood transfusion when necessary. The mortality in 74 of his cases was 24 per cent, and in 14 of his severe cases was as high as 43 per cent, showing that some very potent factor was missing from the line of the recognized routine treatment. Miller and Studdert (1942) draw attention to 5 Newcastle cases which failed to show any significant response to normal diet plus marmite and refined and crude liver extracts but responded to raw liver by mouth. Davidson, Davis and Innes (1942) give details of 16 cases of macrocytic anæmia of pregnancy, 10 of which did not yield to massive doses of liver extract. Two of them proved fatal while ultimate response was

obtained in 8 cases when iron, yeast and ascorbic acid were added to the treatment and life was maintained by blood transfusions during the refractory period. Fullerton (1943) records 3 cases of macrocytic anæmia of pregnancy which proved refractory to intensive parenteral liver but yielded rapidly to whole liver. Fullerton believes that there are some unknown anti-anæmic factors in the whole liver that act so rapidly in such refractory cases. I would like here to emphasize that in Davidson, Davis and Innes' (1942) 8 refractory cases whole liver was not given but it was probably yeast that ultimately gave the satisfactory results. The unknown factor, therefore, appears to be common to both the whole liver and yeast. In discussing macrocytic anæmias other than those of pregnancy, Davidson (1939) recorded a case of macrocytic anæmia associated with steatorrhœa which did not respond to parenteral liver extracts alone but did so when high protein diet including ½ pound of whole liver was added to it. Davidson tends to attribute the response to high protein diet, but Fullerton (1943) appears to suggest, and I agree with him, that the improvement in Davidson's case was probably due to the inclusion of ½ pound of whole liver daily to the high protein diet. Taylor and Manchanda (1940) treated 24 cases of 'tropical macrocytic anæmia' with parenteral liver, marmite and yeast and lost only one case —a mortality of 4.2 per cent. They, however, failed to understand why two of their cases remained macrocytic for two and three months and did not yield to 'intensive treatment by liver injections, marmite and blood transfusion'. They apparently did not give yeast to these two of their cases. Ungley and James (1934) reported that, in 10 of their 18 cases, massive doses of yeast extract given by mouth produced a hæmopoietic response but the same extract given parenterally did not. Napier (1936) also found that yeast extract given by mouth cured tropical macrocytic anæmia and noted (1939) that a yeast extract given even parenterally appeared to have a curative effect in one of his cases. Napier (1936) finding cases resistant to routine treatment put forward an idea that tropical macrocytic anæmias might be due to the deficiency of an 'independent hæmopoietic principle' and later on (1939) believed that it was not identical with Castle's extrinsic factor. Fairley and his co-workers (1938) had sufficient evidence to divide their cases of tropical macrocytic anæmia into hæmolytic and non-hæmolytic group. Napier and Majumdar (1938), supporting that view, came to the conclusion that macrocytic anæmia may be produced by a 'relative deficiency in important food factor probably associated with vitamin B_2 complex' and that this deficiency may be determined by excessive hæmolysis in an individual on a border-line diet due to malaria or other similar conditions. Napier (1939) came very near the truth when he definitely stated that such cases may be due to a deficiency in B_2 complex and that yeast and crude liver probably contain his 'additional hæmopoietic factor'. He, however, failed to identify the deficient substance but in order to get it identified he very rightly suggested that 'careful quantitative work with only purified fractions of autolyzed yeast and liver extracts seems to offer the best prospects'. For the last 4 years I have been using nicotinic acid in the treatment of refractory cases of macrocytic anæmia associated with pregnancy, pellagra, steatorrhœa and other conditions, with almost dramatic results. The short notes of the illustrative cases cited above, the details of some of which have already appeared in other journals, show that nicotinic acid can act independently of liver and yeast. It will thus be seen that not only the macrocytic anæmia of pregnancy but of all varieties may prove at one time or other refractory to parenteral liver, marmite and high protein diet but yield to whole liver, yeast or nicotinic acid. As these three substances have given satisfactory results independently in different hands, and as whole liver and yeast are both very rich sources of nicotinic acid, I am inclined to believe that nicotinic acid is the factor, or one of the essentially active factors, which really acts when cases refractory to parenteral liver and marmite respond to whole liver or yeast, and which Fullerton believed to be present in the whole liver and Napier in autolyzed yeast. It may, however, be noted that this resistance to parenteral liver generally develops either late in the first attack or at some time during the recurrence of the disease. It is, therefore, justifiable to assume that it is the depletion of nicotinic acid which at a certain stage and intensity interferes either with the secretion of the intrinsic factor or with the combination of it with the extrinsic factor and makes a case refractory to ordinary therapy. Nicotinic acid is now recognized to be responsible for the maintenance of growth, health and nourishment of epithelial tissues in the body. Its deficiency as noted in pellagrins causes atrophic type of degeneration of epithelial cells. It is, therefore, not difficult to see how it could affect the gastric function and the secretion of gastric hydrochloric acid and Castle's intrinsic factor, and how it could interfere with the combination and absorption of the hæmopoietic principle in the gastro-intestinal tract. The meagreness and limitations of my clinical work and observations are obvious, but the research has been done with a definite purpose in view and in as scientific and systematic a manner as possible. Further work with nicotinic acid in such cases by those who have better facilities is, therefore, clearly indicated.

Summary.—Clinical evidence has been brought forward to prove that nicotinic acid deficiency may occur in cases of macrocytic anæmia associated with pregnancy or with any other condition, and that nicotinamide depletion

in the body can reach a stage when the supply of known anti-anæmia factors, in the form of parenteral liver extract and marmite, cannot produce blood regeneration ; in such cases the exhibition of nicotinic acid singly or in combination with other routine treatments may act almost in a dramatic fashion in bringing the blood picture to normal.

It is suggested that nicotinic acid is the factor that acts when cases refractory to parenteral liver rapidly yield to whole liver or yeast.

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LATENT TUBERCULOSIS IN MEDICAL STUDENTS OF THE KING EDWARD MEDICAL COLLEGE, LAHORE, PUNJAB

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WITH the interest in mass miniature radiography in India, this report is submitted for publication, in an incomplete state. The work was interrupted by recall to military service.

The work was planned for a five-year period with a follow-up of positive cases.

For 3 years from 1938 to 1940, medical students of the King Edward Medical College, Lahore, India, were subjected to yearly examination by the intradermal injections of international standard tuberculin solutions of 1/1,000 strength, which had been freshly prepared. The technique used was the standard one of the Tuberculosis Association of India based on the Mantoux reaction. In some cases negative-reacting students were re-examined with a 1/100 solution. Full-size skiagrams of the chests of the first-year medical students were taken during their first year of college attendance. Those with positive films were subsequently investigated clinically, and, where necessary, frequent later skiagrams were taken.

The students were Moslem, Sikh and Hindu, their numbers being according to the communal representation of the province.

The results of the Mantoux reactions obtained are shown in table I.

The following conclusions and observations were made :—

(1) On admission to the college, students gave a high rate of positive Mantoux reactions, 51 per cent of the total first year in 1939 and 68.5 per cent in 1940 being positive. High rates had been obtained among Lahore school children.

(2) The incidence of positive reactors rose in the fifth-year medical students to 86 per cent in 1938 and 98 per cent in 1939.

(3) The largest rise in the percentage of positive reactions took place between the third and fourth years, when students begin work in the medical, surgical and tuberculosis wards.

(4) No cases of radiologically or clinically active tuberculosis developed during this period in the students who developed a positive Mantoux reaction after being earlier negative. Skiagrams of the chest of such students were taken as a routine. It is now a commonplace that primary tuberculosis is, in the vast majority of people, of the mildest nature and is often not accompanied by clinical signs or symptoms. These students were unaware of any illnesses, though some complained of coughs and colds.

(5) Twenty students who had shown positive reactions later showed negative ones. This change is recorded in the literature of the Mantoux reaction. Its significance is not fully understood.

(6) Fifteen per cent of the positive reactions were of the severe +++ or ++++ type (with ulceration). These reactions led to much discussion, but no conclusions were reached.

The results of the skiagrams of the chest are shown in table II.

Looking back on this work, I now think that the interpretation of the group 'positive skiagrams without toxæmia' may need revision in future work of this nature. It is notoriously difficult to interpret films of early chest tuberculosis. There may have been an inclination towards reporting positive findings when now, with more experience, negative results would be reported. But in two students in whom active clinical tuberculosis in fact developed in 1940, the early radiological signs at the apices of the films had been missed at the first examination when the students were examined in an apparently healthy state in 1938. Subsequent examination of the first films (1938) showed early disease.

On admission to the college, students were medically examined, but this examination did